FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
55865	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
not yet assigned 09/830706	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP99/05983	October 28, 1999	October 30, 1998

TITLE OF INVENTION
THIOREDOXIN REDUCTASE II

APPLICANT(S) FOR DO/EO/US
Shingo,TOJI; Minoru YANO; Katsuyuki TAMAI

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☒ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copyof PCT Request; Copy of PCT Demand; all other papers which have been received from teh international Bureau

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
not yet assigned 09/830706	PCT/JP99/05983	55865

24. The following fees are submitted:.	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$130.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	19 - 20 =	0	x $18.00	**$0.00**
Independent claims	10 - 3 =	7	x $80 00	**$560.00**
Multiple Dependent Claims **(check if applicable).**			☒	**$270.00**
TOTAL OF ABOVE CALCULATIONS =				**$1,820.00**
☒ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$910.00**
SUBTOTAL =				**$910.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**
TOTAL NATIONAL FEE =				**$910.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**
TOTAL FEES ENCLOSED =				**$910.00**
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of **$910.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **04-1105** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Peter F. Corless
Dike, Bronstein, Roberts & Cushman
Intellectual Property Pract Group
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boaton, MA 02209

SIGNATURE

Peter F. Corless
NAME

33,860
REGISTRATION NUMBER

April 26, 2001
DATE

55865(71965)
Docket No. ~~49960 (71526)~~

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	S. Toji et al.		
Application No.:	09/830,706	Group No.:	Not Yet Assigned
Filed:	August 7, 2001	Examiner:	Not Yet Assigned
For:	THIOREDOXIN REDUCTASE II		

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT

Please amend the above-identified application as follows.

IN THE SPECIFICATION

On page 9, line 27, after "TxR" insert --(SEQ ID NOS:2 and 38)--.

On page 21, line 7, after "Figure 1" insert --(SEQ ID NOS:2 and 38)--.

On page 22, line 3, after "(32mer))" insert --(SEQ ID NO:6)--.

On page 22, line 9, after "(32 mer))" insert --(SEQ ID NO:7)--.

On page 29, line 4, after "Figure 1,", delete "SEQ ID NO: 1" and insert --SEQ ID NO:1/2--.

On page 29, line 27, after "GTC-3'", insert --(SEQ ID NO:8)--.

On page 29, line 28, after "TTC-3'", insert --(SEQ ID NO:9)--.

On page 30, line 36, after "CTC-3'", insert --(SEQ ID NO:10)--.

On page 31, line 1, after "CAC-3'", insert --(SEQ ID NO:11)--.

On page 31, line 3, after "TAC-3'", insert --(SEQ ID NO:12)--.

REMARKS

The specification at pages 9, 21, 22, 29, 30 and 31 have been amended to include the SEQ ID NOS. A copy of the application with these amendments is enclosed herewith. No new matter has been added.

Respectfully submitted,

Peter F. Corless (Reg. No. 33,860)
Edwards & Angell, LLP
P.O. Box 9169
Boston, MA 02209
(617) 439-4444

Date: September 24, 2001

Practitioner's Docket No. 55865 (71131) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Shingo TOJI et al.
Application No.: not yet assigned
Filed: Herewith
For: THIOREDOXIN REDUCTASE II

Group No.: not yet assigned
Examiner: Not yet assigned

Box Sequence
Assistant Commissioner for Patents
Washington, D.C. 20231

SUBMISSION OF "SEQUENCE LISTING," COMPUTER READABLE COPY, AND/OR AMENDMENT PERTAINING THERETO FOR BIOTECHNOLOGY INVENTION CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE

(check and complete this item, if applicable)

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*
*(When using Express Mail, the Express Mail label number is **mandatory**;*
Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

37 C.F.R. § 1.8(a)

☐ with sufficient postage as first class mail.

37 C.F.R. § 1.10*

☒ as "Express Mail Post Office to Address" Mailing Label No. EL196832297US **(mandatory)**

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

Signature Laura M. McGuire

Date: April 27, 2001

Laura M. McGuire

(type or print name of person certifying)

***WARNING:** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight

1. [ ] This replies to the Office Letter DATED _____.

NOTE: If these papers are filed before the office letter issues, adequate identification of the original papers should be made, e.g., in addition to the name of the inventor and title of invention, the filing date based on the "Express Mail" procedure, the serial number from the return post card or the attorney's docket number added

[X] A copy of the Office Letter is enclosed.

IDENTIFICATION OF PERSON MAKING STATEMENT

2. I, Peter F. Corless
(type or print name of person signing below)

state the following:

ITEMS BEING SUBMITTED

3. Submitted herewith is/are

(check each item as applicable)

A. [X] "Sequence Listing(s)" for the nucleotide and/or amino acid sequence(s) in this application. Each "Sequence Listing" is assigned a separate identifier as required in 37 C.F.R. § 1.821(c) and 37 C.F.R. §§ 1.822 and 1.823.

B. [ ] An amendment to the description and/or claims, wherein reference is made to the sequence by use of the assigned identifier, as required in 37 C.F.R. § 1.821(d).

C. [X] A copy of each "Sequence Listing" submitted for this application in computer readable form, in accordance with the requirements of 37 C.F.R. §§ 1.821(e) and 1.824.

D. [ ] Please transfer to this application, in accordance with 37 C.F.R. § 1.821(e), the computer readable copy(ies) from applicant's other application identified as follows:

In re application of:
Application No.: 0 /
Filed:
For:

Group No.:
Examiner:

The Computer readable form(s) of applicant's other application corresponds to the "Sequence Identifier(s)" of the application as follows:

Computer Readable Form	"Sequence Identifier"
(other application)	(this application)

NOTE: "If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Office, reference maybe made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application. The new application shall be accompanied by a letter making such reference to the other application and computer readable form, both of which shall be completely identified." 37 C.F.R. § 1.821(e).

E. [X] A statement that the content of each "Sequence Listing" submitted and each computer readable copy are the same, as required in 37 C.F.R. § 1.821(g).

[ ] Because the statement is not made by a person registered to practice before the Office, the Statement is verified as required in 37 C.F.R. § 1.821(b).

F. [ ] Because this submission is made in fulfilling the requirement under 37 C.F.R. § 1.821(g), a statement that the submission includes no new matter.

[ ] Because the statement is not made by a person registered to practice before the Office, the statement is verified, as required in 37 C.F.R. § 1.821(g).

STATEMENT THAT "SEQUENCE LISTING"
AND COMPUTER READABLE COPY ARE THE SAME
AND/OR THAT PAPERS SUBMITTED INCLUDES NO NEW MATTER

4. I hereby state:

(complete applicable item A and/or B)

A. [X] Each computer readable form submitted in this application, including those forms requested to be transferred from applicant's other application, is the same as the "Sequence Listing" to which it is indicated to relate.

B. [ ] All papers accompanying this submission, or for which a request for transfer from applicants' other application, introduce no new matter.

STATUS

5. Applicant is

[X]a small entity. A statement:

[ ] is attached.

[ ] was already filed.

[ ] other than a small entity.

EXTENSION OF TERM

6.

NOTE: "Extension of Time in Patent Cases (Supplement Amendments) If a timely and complete response has been filed after a Non-Final Office Action, an extension of time is not required to permit filing and/or entry of an additional amendment after expiration of the shortened statutory period.

If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run." Notice of Dec.10, 1985 (1061 O.G. 34-35).

NOTE: See 37 C.F.R. § 1.645 for extensions of time in interference proceedings and 37 C.F.R. § 1.550(c) for extensions of time in reexamination proceedings.

7. The proceedings herein are for a patent application and the provisions of 37 C.F.R. § 1.136 apply.

(complete (a) or (b) as applicable)

(a) [ ] Applicant petitions for an extension of time under 37 C.F.R. § 1.136 (fees: 37 C.F.R. § 1.17(a)(1)-(4)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
[ ]	one month	$110.00	$ 55.00
[ ]	two months	$390.00	$ 195.00
[ ]	three months	$890.00	$ 445.00
[ ]	four months	$1,390.00	$ 695.00

Fee $ _____

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured, and the fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $_____

OR

(b) [X] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

FEE PAYMENT

8. [ ] Attached is a check in the sum of $ _____.

[ ] Charge Account No. _____ the sum of $ _____.
A duplicate of this transmittal is attached.

FEE DEFICIENCY

9.

NOTE: If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, 1065 O.G. 31-33.

10. [X] If any additional extension and/or fee is required, charge Account No. 04-1105 .

SIGNATURE(s)

Peter F. Corless
(type or print name of person signing statement)

Signature

April 26, 2001
Date
EDWARDS & ANGELL, LLP
DIKE, BRONSTEIN, ROBERTS & CUSHMAN
Intellectual Property Practice Group
P. O. Box 9169, Boston, MA 02209
P.O. Address of Signatory

(If applicable)

Tel. No.: (617) 523-3400
Fax No.: (617) 523-6440
Customer No. 21874

[ ] Inventor
[ ] Assignee of complete interest
[ ] Person authorized to sign on behalf of assignee
[X] Practitioner of record
[ ] Filed under Rule 34(a)
[X] Registration No. 33,860
[ ] Other
(specify identity of person signing)

(complete the following, if applicable)

_____
(type name of assignee)

_____
Address of assignee

_____

_____
Title of person authorized to sign on behalf of assignee

A "STATEMENT UNDER 37 C.F.R. 3.73(b)" is attached.

Assignment recorded in PTO on _____
Reel _____ Frame _____

_____
SIGNATURE OF PRACTITIONER

Reg. No.

_____
(type or print name of practitioner)

Tel. No.: ( )

_____
P.O. Address

Customer No.:

_____

SEQUENCE LISTING

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Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr Arg Trp Gly Leu Gly
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            100                 105                 110

Glu Val Ala Gln Pro Val Pro His Asp Trp Arg Lys Met Ala Glu Ala
        115                 120                 125

Val Gln Asn His Val Lys Ser Leu Asn Trp Gly His Arg Val Gln Leu
    130                 135                 140

Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys Ala Ser Phe Val Asp
145                 150                 155                 160

Glu His Thr Val Cys Gly Val Ala Lys Gly Gly Lys Glu Ile Leu Leu
                165                 170                 175

Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly Arg Pro Arg Tyr Pro
```

180 185 190

Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile Thr Ser Asp Asp Ile
195 200 205

Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu Val Val Gly Ala Ser
210 215 220

Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr Gly Ile Gly Leu Asp
225 230 235 240

Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg Gly Phe Asp Gln Gln
245 250 255

Met Ser Ser Met Val Ile Glu His Met Ala Ser His Gly Thr Arg Phe
260 265 270

Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg Leu Pro Asp Gly Gln
275 280 285

Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly Lys Glu Asp Thr Gly
290 295 300

Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg Val Pro Asp Thr Arg
305 310 315 320

Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr Ser Pro Asp Thr Gln
325 330 335

Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser Val Pro His Ile Tyr
340 345 350

Ala Ile Gly Asp Val Val Glu Gly Arg Pro Glu Leu Thr Pro Thr Ala
355 360 365

Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu Phe Gly Gly Ser Ser
370 375 380

Asp Leu Met Asp Tyr Asp Asn Val Pro Thr Thr Val Phe Thr Pro Leu
385 390 395 400

Glu Tyr Gly Cys Val Gly Leu Ser Glu Glu Glu Ala Val Ala Arg His
405 410 415

Gly Gln Glu His Val Glu Val Tyr His Ala His Tyr Lys Pro Leu Glu
420 425 430

Phe Thr Val Ala Gly Arg Asp Ala Ser Gln Cys Tyr Val Lys Met Val
435 440 445

Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly Leu His Phe Leu Gly
450 455 460

Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala Leu Gly Ile Lys Cys
465 470 475 480

Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val Gly Ile His Pro Thr

```
                485                 490                 495

Cys Ser Glu Glu Val Val Lys Leu Arg Ile Ser Lys Arg Ser Gly Leu
            500                 505                 510

Asp Pro Thr Val Thr Gly Cys Xaa Gly
        515                 520


<210> 3
<211> 2056
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (188)..(1669)
<223> tga(1664)..(1666) is transrated to selenosysteine, shown by Xaa.

<400> 3
gtcccggacc tcaggcccag ttcagtgtac ttcccctctc tacttcctcc ctccagtccc 60

ttctccatcc ctccctttt tggctgcccc ttgcctgcct tcctcgccag tagcttgcag 120

agtagacacg atgacacctt ttgcaggcta aaaaggctga gagtggcact atgtgcagtg 180

agccacc atg gag gac caa gca ggt cag cgg gac tat gat ctc ctg gtg   229
        Met Glu Asp Gln Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val
          1               5                  10

gtc ggc ggg gga tct ggt ggc ctg gct tgt gcc aag gag gcc gcc cag   277
Val Gly Gly Gly Ser Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln
 15                  20                  25                  30

ctg gga agg aag gtg gcc gtg gtg gac tac gtg gaa cct tct ccc caa   325
Leu Gly Arg Lys Val Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln
                35                  40                  45

ggc acc cgg tgg ggc ctc ggc ggc acc tgc gtc aac gtg ggc tgc atc   373
Gly Thr Arg Trp Gly Leu Gly Gly Thr Cys Val Asn Val Gly Cys Ile
            50                  55                  60

ccc aag aag ctg atg cac cag gcg gca ctg ctg gga ggc ctg atc caa   421
Pro Lys Lys Leu Met His Gln Ala Ala Leu Leu Gly Gly Leu Ile Gln
         65                  70                  75

gat gcc ccc aac tat ggc tgg gag gtg gcc cag ccc gtg ccg cat gac   469
Asp Ala Pro Asn Tyr Gly Trp Glu Val Ala Gln Pro Val Pro His Asp
     80                  85                  90

tgg agg aag atg gca gaa gct gtt caa aat cac gtg aaa tcc ttg aac   517
Trp Arg Lys Met Ala Glu Ala Val Gln Asn His Val Lys Ser Leu Asn
 95                  100                 105                 110

tgg ggc cac cgt gtc cag ctt cag gac aga aaa gtc aag tac ttt aac   565
Trp Gly His Arg Val Gln Leu Gln Asp Arg Lys Val Lys Tyr Phe Asn
                115                 120                 125
```

```
atc aaa gcc agc ttt gtt gac gag cac acg gtt tgc ggc gtt gcc aaa   613
Ile Lys Ala Ser Phe Val Asp Glu His Thr Val Cys Gly Val Ala Lys
            130                 135                 140

ggt ggg aaa gag att ctg ctg tca gcc gat cac atc atc att gct act   661
Gly Gly Lys Glu Ile Leu Leu Ser Ala Asp His Ile Ile Ile Ala Thr
        145                 150                 155

gga ggg cgg ccg aga tac ccc acg cac atc gaa ggt gcc ttg gaa tat   709
Gly Gly Arg Pro Arg Tyr Pro Thr His Ile Glu Gly Ala Leu Glu Tyr
    160                 165                 170

gga atc aca agt gat gac atc ttc tgg ctg aag gaa tcc cct gga aaa   757
Gly Ile Thr Ser Asp Asp Ile Phe Trp Leu Lys Glu Ser Pro Gly Lys
175                 180                 185                 190

acg ttg gtg gtc ggg gcc agc tat gtg gcc ctg gag tgt gct ggc ttc   805
Thr Leu Val Val Gly Ala Ser Tyr Val Ala Leu Glu Cys Ala Gly Phe
                195                 200                 205

ctc acc ggg att ggg ctg gac acc acc atc atg atg cgc agc atc ccc   853
Leu Thr Gly Ile Gly Leu Asp Thr Thr Ile Met Met Arg Ser Ile Pro
            210                 215                 220

ctc cgc ggc ttc gac cag caa atg tcc tcc atg gtc ata gag cac atg   901
Leu Arg Gly Phe Asp Gln Gln Met Ser Ser Met Val Ile Glu His Met
        225                 230                 235

gca tct cat ggc acc cgg ttc ctg agg ggc tgt gcc ccc tcg cgg gtc   949
Ala Ser His Gly Thr Arg Phe Leu Arg Gly Cys Ala Pro Ser Arg Val
    240                 245                 250

agg agg ctc cct gat ggc cag ctg cag gtc acc tgg gag gac agc acc   997
Arg Arg Leu Pro Asp Gly Gln Leu Gln Val Thr Trp Glu Asp Ser Thr
255                 260                 265                 270

acc ggc aag gag gac acg ggc acc ttt gac acc gtc ctg tgg gcc ata  1045
Thr Gly Lys Glu Asp Thr Gly Thr Phe Asp Thr Val Leu Trp Ala Ile
                275                 280                 285

ggt cga gtc cca gac acc aga agt ctg aat ttg gag aag gct ggg gta  1093
Gly Arg Val Pro Asp Thr Arg Ser Leu Asn Leu Glu Lys Ala Gly Val
            290                 295                 300

gat act agc ccc gac act cag aag atc ctg gtg gac tcc cgg gaa gcc  1141
Asp Thr Ser Pro Asp Thr Gln Lys Ile Leu Val Asp Ser Arg Glu Ala
        305                 310                 315

acc tct gtg ccc cac atc tac gcc att ggt gac gtg gtg gag ggg cgg  1189
Thr Ser Val Pro His Ile Tyr Ala Ile Gly Asp Val Val Glu Gly Arg
    320                 325                 330

cct gag ctg aca ccc aca gcg atc atg gcc ggg agg ctc ctg gtg cag  1237
Pro Glu Leu Thr Pro Thr Ala Ile Met Ala Gly Arg Leu Leu Val Gln
335                 340                 345                 350
```

```
cgg ctc ttc ggc ggg tcc tca gat ctg atg gac tac gac aat gtt ccc   1285
Arg Leu Phe Gly Gly Ser Ser Asp Leu Met Asp Tyr Asp Asn Val Pro
                355                 360                 365

acg acc gtc ttc acc cca ctg gag tat ggc tgt gtg ggg ctg tcc gag   1333
Thr Thr Val Phe Thr Pro Leu Glu Tyr Gly Cys Val Gly Leu Ser Glu
            370                 375                 380

gag gag gca gtg gct cgc cac ggg cag gag cat gtt gag gtc tat cac   1381
Glu Glu Ala Val Ala Arg His Gly Gln Glu His Val Glu Val Tyr His
        385                 390                 395

gcc cat tat aaa cca ctg gag ttc acg gtg gct gga cga gat gca tcc   1429
Ala His Tyr Lys Pro Leu Glu Phe Thr Val Ala Gly Arg Asp Ala Ser
    400                 405                 410

cag tgt tat gta aag atg gtg tgc ctg agg gag ccc cca cag ctg gtg   1477
Gln Cys Tyr Val Lys Met Val Cys Leu Arg Glu Pro Pro Gln Leu Val
415                 420                 425                 430

ctg ggc ctg cat ttc ctt ggc ccc aac gca ggc gaa gtt act caa gga   1525
Leu Gly Leu His Phe Leu Gly Pro Asn Ala Gly Glu Val Thr Gln Gly
                435                 440                 445

ttt gct ctg ggg atc aag tgt ggg gct tcc tat gcg cag gtg atg cgg   1573
Phe Ala Leu Gly Ile Lys Cys Gly Ala Ser Tyr Ala Gln Val Met Arg
            450                 455                 460

acc gtg ggt atc cat ccc aca tgc tct gag gag gta gtc aag ctg cgc   1621
Thr Val Gly Ile His Pro Thr Cys Ser Glu Glu Val Val Lys Leu Arg
        465                 470                 475

atc tcc aag cgc tca ggc ctg gac ccc acg gtg aca ggc tgc tga ggg   1669
Ile Ser Lys Arg Ser Gly Leu Asp Pro Thr Val Thr Gly Cys Xaa Gly
    480                 485                 490

taagcgccat ccctgcaggc cagggcacac ggtgcgcccg ccgccagctc ctcggaggcc 1729

agacccagga tggctgcagg ccaggtttgg ggggcctcaa ccctctcctg gagcgcctgt 1789

gagatggtca gcgtggagcg caagtgctgg acgggtggcc cgtgtgcccc acagggatgg 1849

ctcaggggac tgtccacctc acccctgcac ctttcagcct ttgccgccgg gcacccccc 1909

caggctcctg gtgccggatg atgacgacct gggtggaaac ctaccctgtg ggcacccatg 1969

tccgagcccc ctggcatttc tgcaatgcaa ataaagaggg tacttttttct gaagtgtgta 2029

aaaaaaaaaa aaaaaaaaaa aaaaaaa                                      2056
```

<210> 4
<211> 492
<212> PRT
<213> Homo sapiens
<223> Xaa(493) means selenosysteine.

<400> 4

```
Met Glu Asp Gln Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val Val Gly
 1               5                  10                  15

Gly Gly Ser Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln Leu Gly
            20                  25                  30

Arg Lys Val Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr
        35                  40                  45

Arg Trp Gly Leu Gly Gly Thr Cys Val Asn Val Gly Cys Ile Pro Lys
    50                  55                  60

Lys Leu Met His Gln Ala Ala Leu Leu Gly Gly Leu Ile Gln Asp Ala
65                  70                  75                  80

Pro Asn Tyr Gly Trp Glu Val Ala Gln Pro Val Pro His Asp Trp Arg
                85                  90                  95

Lys Met Ala Glu Ala Val Gln Asn His Val Lys Ser Leu Asn Trp Gly
            100                 105                 110

His Arg Val Gln Leu Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys
        115                 120                 125

Ala Ser Phe Val Asp Glu His Thr Val Cys Gly Val Ala Lys Gly Gly
    130                 135                 140

Lys Glu Ile Leu Leu Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly
145                 150                 155                 160

Arg Pro Arg Tyr Pro Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile
                165                 170                 175

Thr Ser Asp Asp Ile Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu
            180                 185                 190

Val Val Gly Ala Ser Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr
        195                 200                 205

Gly Ile Gly Leu Asp Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg
    210                 215                 220

Gly Phe Asp Gln Gln Met Ser Ser Met Val Ile Glu His Met Ala Ser
225                 230                 235                 240

His Gly Thr Arg Phe Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg
                245                 250                 255

Leu Pro Asp Gly Gln Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly
            260                 265                 270

Lys Glu Asp Thr Gly Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg
        275                 280                 285

Val Pro Asp Thr Arg Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr
    290                 295                 300
```

Ser Pro Asp Thr Gln Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser
305 310 315 320

Val Pro His Ile Tyr Ala Ile Gly Asp Val Val Glu Gly Arg Pro Glu
325 330 335

Leu Thr Pro Thr Ala Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu
340 345 350

Phe Gly Gly Ser Ser Asp Leu Met Asp Tyr Asp Asn Val Pro Thr Thr
355 360 365

Val Phe Thr Pro Leu Glu Tyr Gly Cys Val Gly Leu Ser Glu Glu Glu
370 375 380

Ala Val Ala Arg His Gly Gln Glu His Val Glu Val Tyr His Ala His
385 390 395 400

Tyr Lys Pro Leu Glu Phe Thr Val Ala Gly Arg Asp Ala Ser Gln Cys
405 410 415

Tyr Val Lys Met Val Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly
420 425 430

Leu His Phe Leu Gly Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala
435 440 445

Leu Gly Ile Lys Cys Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val
450 455 460

Gly Ile His Pro Thr Cys Ser Glu Glu Val Val Lys Leu Arg Ile Ser
465 470 475 480

Lys Arg Ser Gly Leu Asp Pro Thr Val Thr Gly Cys Xaa Gly
485 490

<210> 5
<211> 130
<212> DNA
<213> Homo sapiens

<400> 5
tcagcctttg ccgccgggca ccccccccag gctcctggtg ccggatgatg acgacctggg 60

tggaaaccta ccctgtgggc acccatgtcc gagccccctg gcatttctgc aatgcaaata 120

aagagggtac 130

<210> 6
<211> 32
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:Synthesis

<400> 6
gcgggatcca tgacttttaa cagttttgaa gg 32

<210> 7
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Synthesis

<400> 7
gcgctcgagc tactatagag ttagattaag ac 32

<210> 8
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 8
tatgatctcc tggtggtc 18

<210> 9
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Synthesis

<400> 9
gtcatcactt gtgattcc 18

<210> 10
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Synthesis

<400> 10
acagcttctg ccatcttcct c 21

<210> 11
<211> 21
<212> DNA

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Synthesis

<400> 11
agaaggttcc acgtagtcca c 21

<210> 12
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:Synthesis

<400> 12
ccatacgatg ttccagatta c 21

<210> 13
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 13
acgatggcgg caatggcggt g 21

<210> 14
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 14
accatggagg accaagcagg t 21

<210> 15
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 15
ttaccctcag cagcctgtca c 21

<210> 16
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 16
gcgccatccc tgcaggccag g 21

<210> 17
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:synthesis

<400> 17
cacacttcag aaaaagtacc c 21

<210> 18
<211> 103
<212> DNA
<213> Homo sapiens

<400> 18
atggcggcaa tggcggtggc gctgcgggga ttaggagggc gcttccggtg gcggacgcag 60

gccgtggcgg gcggggtgcg gggcgcggcg cggggcgcag cag 103

<210> 19
<211> 200
<212> DNA
<213> Homo sapiens

<400> 19
gtcccggacc tcaggcccag ttcagtgtac ttcccctctc tacttcctcc ctccagtccc 60

ttctccatcc ctccctttt tggctgcccc ttgcctgcct tcctcgccag tagcttgcag 120

agtagacacg atgacacctt ttgcaggcta aaaaggctga gagtggcact atgtgcagtg 180

agccaccatg gaggaccaag 200

<210> 20
<211> 69
<212> DNA
<213> Homo sapiens

<400> 20
caggtcagcg ggactatgat ctcctggtgg tcggcggggg atctggtggc ctggcttgtg 60

ccaaggagg 69

<210> 21
<211> 57
<212> DNA
<213> Homo sapiens

<400> 21
ccgcccagct gggaaggaag gtggtggtgg tggactacgt ggaaccttct ccccaag 57

<210> 22
<211> 145
<212> DNA
<213> Homo sapiens

<400> 22
gcacccggtg gggcctcggc ggcacctgcg tcaacgtggg ctgcatcccc aagaagctga 60

tgcaccaggc ggcactgctg ggaggcctga tccaagatgc ccccaactat ggctgggagg 120

tggcccagcc cgtgccgcat gactg 145

<210> 23
<211> 75
<212> DNA
<213> Homo sapiens

<400> 23
gaggaagatg gcagaagctg ttcaaaatca cgtgaaatcc ttgaactggg gccaccgtgt 60

ccagcttcag gacag 75

<210> 24
<211> 79
<212> DNA
<213> Homo sapiens

<400> 24
aaaagtcaag tactttaaca tcaaagccag ctttgttgac gagcacacgg tttgcggcgt 60

tgccaaaggt gggaaagag 79

<210> 25
<211> 63
<212> DNA
<213> Homo sapiens

<400> 25
attctgctgt cagccgatca catcatcatt gctactggag ggcggccgag ataccccacg 60

cac 63

<210> 26
<211> 71
<212> DNA
<213> Homo sapiens

<400> 26
atcgaaggtg ccttggaata tggaatcaca agtgatgaca tcttctggct gaaggaatcc 60

cctggaaaaa c 71

<210> 27
<211> 20
<212> DNA
<213> Homo sapiens

<400> 27
gttggtggtc ggggccagct 20

<210> 28
<211> 92
<212> DNA
<213> Homo sapiens

<400> 28
atgtggccct ggagtgtgct ggcttcctca ccgggattgg gctggacacc accatcatga 60

tgcgcagcat ccccctccgc ggcttcgacc ag 92

<210> 29
<211> 175
<212> DNA
<213> Homo sapiens

<400> 29
caaatgtcct ccatggtcat agagcacatg gcatctcatg gcacccggtt cctgaggggc 60

tgtgcccccc cgcgggtcag gaggctccct gatggccagc tgcaggtcac ctgggaggac 120

agcaccaccg gcaaggagga cacgggcacc tttgacaccg tcctgtgggc catag 175

<210> 30
<211> 137
<212> DNA
<213> Homo sapiens

<400> 30
gtcgagtccc agacaccaga agtctgaatt tggagaaggc tggggtagat actagccccg 60

acactcagaa gatcctggtg gactcccggg aagccacctc tgtgccccac atctacgcca 120

ttggtgacgt ggtggag 137

<210> 31
<211> 96
<212> DNA
<213> Homo sapiens

<400> 31
gggcggcctg agctgacacc cacagcgatc atggccggga ggctcctggt gcagcggctc 60

ttcggcgggt cctcagatct gatggactac gacaat 96

<210> 32
<211> 93
<212> DNA
<213> Homo sapiens

<400> 32
gttcccacga ccgtcttcac cccactggag tatggctgtg tggggctgtc cgaggaggag 60

gcagtggctc gccacgggca ggagcatgtt gag 93

<210> 33
<211> 72
<212> DNA
<213> Homo sapiens

<400> 33
gtctatcacg cccattataa accactggag ttcacggtgg ctggacgaga tgcatcccag 60

tgttatgtaa ag 72

<210> 34
<211> 98
<212> DNA
<213> Homo sapiens

<400> 34
atggtgtgcc tgagggagcc cccacagctg gtgctgggcc tgcatttcct tggccccaac 60

gcaggcgaag ttactcaagg atttgctctg gggatcaa 98

<210> 35
<211> 195
<212> DNA
<213> Homo sapiens

<400> 35
gtgtggggct tcctatgcgc aggtgatgcg gaccgtgggt atccatccca catgctctga 60

ggaggtagtc aagctgcgca tctccaagcg ctcaggcctg gaccccacgg tgacaggctg 120

ctgagggtaa gcgccatccc tgcaggccag ggcacacggt gcgcccgccg ccagctcctc 180

ggaggccaga cccag 195

<210> 36
<211> 290
<212> DNA
<213> Homo sapiens

<400> 36
gatggctgca ggccaggttt gggggggcctc aaccctctcc tggagcgcct gtgagatggt 60

cagcgtggag cgcaagtgct ggacgggtgg cccgtgtgcc ccacagggat ggctcagggg 120

actgtccacc tcacccctgc acctttcagc ctttgccgcc gggcaccccc cccaggctcc 180

tggtgccgga tgatgacgac ctgggtggaa acctaccctg tgggcaccca tgtccgagcc 240

ccctggcatt tctgcaatgc aaataaagag ggtacttttt ctgaagtgtg 290

<210> 37
<211> 66566
<212> DNA
<213> Homo sapiens

<400> 37
atggcggcaa tggcggtggc gctgcgggga ttaggagggc gcttccggtg gcggacgcag 60

gccgtggcgg gcggggtgcg gggcgcggcg cggggcgcag caggtaggat ggggtcgggg 120

cgtccccgcg gtaggtgtcc gcgcggccgg ggtgtcctcg tgagggtgtc cgcgcggcgg 180

tggccagggt gtccccgtgg gggtgcccac gcgggggtgt ccacataccg gcctcttggt 240

ctagtcttgc tcaggagtcc gggctgcttc tagccacaag tagccccctt cccaggtggg 300

gaaactgggg ctgggtgcct tgtctaaggt cctgctgtgc tgactgcacc tgtggtctcc 360

cagagctggt atcccagtaa caactacagt tctgaagatg atgatatccc acctcccgag 420

gtcaccaggc accggcccca ctggccagac ttcccaactt ctccccagac ccctagactc 480

tagaggttag aggctgcaca gagcaatggg aggatacaca ctcgtcctcc tggagcccct 540

gaagaacagt taactaaatc aggacaataa tcataactga gcactcgaag cagaggctgg 600

gtgtctggtc actcaggaca gttcaagcct catcctgtag gacagactcc cctagatccg 660

accagagcgc caccatatct gttatgtgtg gccagtttca ttccatgcac gacaacatgg 720

tcccccacca tgcagggggc ccctcgaccc agccccctgg atgcttgtga cagcgagcag 780

ctctccccac aggcagtgag tgtagagggg tgtaaggacg gggtcagggc tccttcccag 840

ggatggcggc tatgggaggc atggtggctg gccctctgcc cgcggtggac tcgggaggga 900

gggctgactg tgtgtgtgaa tgggcagagt tggtgctatg gaggttttgg gggtctccag 960

gacggagggt ggcccaacag agttctggga ggcagtcacc acctcgtggc cttgctgaga 1020

cctggaaccc tcagccaggg cactccatct ttcaaagctt cttggctgca tgcgtcaggt 1080

gggcaagctc aggaaggtta aatgcacccg tgctggcgga gtcccataaa aggggattcg 1140

gcatcaaaag gaggaaaaag gttcaaaggg catttatcat ggggttcaga atcacggatg 1200

tgaggggcgg tagtggggac aacagacaga aaagcttccc cttcccatac tcacagtcca 1260

gacacggcaa tagccaaatt ccaaatttct aggtattctg gactcagaat ggggaatatc 1320

atacgagact taggggggata atgcccttat cttcctattt taagggaaag aacaaactga 1380

accttctatg caaaatagga tgatgatcct ggtcctccca gtaagaaata aaataagtag 1440

tctccaggca ttcctttccg ccagaggagc aactgttttt taaatagccc tttcgtgccc 1500

agtctgttac taaaccatat gagttgtttt tttggggttt tttttttttt tttttttttg 1560

agacagtgtc ttgctctgtc gcccaagctg gagtacagtg gtgcgatctc agctcactgc 1620

aagctccgcc tcccgggttc acgccattct cctgcctcag cctcccgagt agctgggact 1680

acaggcatct gccaccacgc ctggctaatt tttttgtat ttttagtaga gacgggattt 1740

cactgtatta gccaggatgg tctcaatctc ctgacctcat gatccacctg ccttggcctc 1800

ccaaagtgct gggattacag gcatgagcca ctgcgcccag ccgagtcatt ttttaatact 1860

actgcatgtg agttaacaca atcattccca aattgaagtt ttagatgggc cctcaaaatt 1920

tttaggatat ggttttccta caggtttata ttgaaagtat ggggtatctc ctattactcc 1980

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DESCRIPTION

THIOREDOXIN REDUCTASE II

Technical Field

The present invention relates to a gene encoding a novel protein having a thioredoxin reductase activity and this protein itself. This protein is likely to closely relate to systems, for example, apoptosis, cancerization, or inflammation and expected to be widely applied to a research material for a therapeutic agent and a diagnostic marker.

Background Art

It is known that viral infection causes apoptosis in cells in a host. This phenomenon is thought to be one of defense mechanisms for removing infected cells from a living body. Against this, viruses furnish an apoptosis inhibitory system for gaining time to proliferate themselves. Namely, an inhibitor of apoptosis protein (IAP) produced by viruses is one of anti-apoptosis proteins which inhibit apoptosis in a host. The presence of homologues for IAP was found in higher animals as well as in viruses. As a human IAP homologue, HIAP1, HIAP2 and XIAP (X-linked Inhibitor of apoptosis protein) have been reported. Among them, HIAP1 and HIAP 2 were clarified to bind to TRAF2 (TNFR associated factor 2) (Cell 83 (7): 1243-52. 1995., Proc Natl Acad Sci USA 94 (19): 10057-62. 1997). On the other hand, any factor binding to XIAP has not been identified yet. In order to analyze functions of XIAP involved in the inhibitory mechanisms of apoptosis in humans, its binding factor is necessary to be identified.

On the other hand, the following has been revealed about thioredoxin reductase (abbreviated to TxR, hereafter). Namely, TxR is involved in DNA transcription mechanism and cancer proliferation through the production of thioredoxin. The following is the reported knowledge.

Thioredoxin reductase; TxR (EC 1.6.4.5) is one of pyridine nucleotide-disulfideoxidoreductase families. This family includes

glutathion reductase, lipoamide dehydrogenase, tripanothion reductase, mercury ion reductase, and NADPH peroxidase. These proteins form a dimer, and have a disulfide bond at a redox active center. Flavin adenine dinucleotide (abbreviated to FAD) is used as co-enzyme to reduce a substrate using reduced form nicotine amide adenine dinucleotide phosphate (abbreviated to NADPH). Thioredoxin reductase oxidizes NADPH to $NADP^+$ and converts oxidized form thioredoxin ($-S_2$) which is a substrate to reduced form thioredoxin $(-SH)_2$ (1). Reduced form thioredoxin reduces a disulfide (S-S) bond in a protein and becomes oxidized form thioredoxin itself (2). Thioredoxin is abbreviated to Trx hereafter.

$NADPH + H^+ + Trx-S_2 \rightarrow NADP^+ + Trx-(SH)_2$ (1)

$Trx-(SH)_2 + protein-S_2 \rightarrow Trx-S_2 + protein-(SH)_2$ (2)

Trx is a redox protein, and plays an important role as an electron donor which creates the reduced state *in vivo*. Trx is an electron donor to an enzyme, for example, ribonucleotide reductase, methionine sulfoxide reductase (Annu. Rev. Biochem 54: 237-71, 1985), vitamin K epoxide reductase (Biochem. Biophys. Res. Commun., 155 (3): 1248-54, 1988). Moreover, Trx catalyses a holding in a protein, and determines a DNA binding capacity of a transcription factor. The following substances are known as a transcription factor in which a DNA biding capacity is controlled by Trx.

NF-κB (J. Biol. Chem. 268 (15): 11380-8. 1993.) (Nucleic Acids Res. 20 (15): 3821-30. 1992)

TFIIIC

BZLF1 (Oncogene 6 (7): 1243-50. 1991.)

Glucocorticoid

p53

In addition, a transcription factor AP-1 is reduced by Ref-1 to have a DNA binding ability, and this Ref-1 is reduced through Trx.

On the other hand, TxR is getting attention as a target for an anticancer agent. For example, secretory type Trx has been reported to have a cytokine-like function and especially reduced form Trx has been reported to be essential for cell proliferation. It is TxR that produces reduced form Trx. Interestingly, in some kind of cancer, concentration of Trx in blood has been reported to increase and TxR

protein has also been reported to increase. It has been reported that insertion of mutation in the Trx redox active center and over expression thereof in oncocytes almost completely inhibited proliferation of oncocytes. From such a background, to terminate proliferation of oncocytes, recently inhibitors of TxR have aggressively been screened. Quinone and nitrosourea, which are anticancer agents, and retinoic acid, which terminates cell proliferation and is a differentiation-inducing agent, have the function of inhibiting TxR.

TxR is a protein containing Se (selenium) which is an essential trace element, as Secys (selenocysteine). Interestingly, Secys is the 21st amino acid which can be translated, and has a unique biosynthetic function by which Secys is encoded by the stop codon UGA. Secys has been also reported to have the radiation protective function and an anticancer effect. As a protein containing Secys, glutathione peroxidase (GPx) which reduces and deletes an active oxygen species hydroperoxide (-OOH), dependently on glutathione and Trx, and type I tetraiodothyronine deiodinase which converts thyroid hormone (thyroxine) precursor T4 into an active form T3, as well as selenoprotein P comprising 10 Secys and selenoprotein W, low molecular weight Secys-containing protein, present in muscles as the proteins which functions have not been well understood, have been reported. The previously reported human TxR has been reported to encode Secys by an amino acid sequence of Cys-Secys-Gly-stop codon (UAA). Absence of the activity of the most understood bovine TxR by treating with carboxypeptidase Y to remove Secys at C-terminus suggested that this C-terminus Secys is reported to be essential for the activity (Zhong, L., E. S. Arn-er, et al. (1998). Rat and calf thioredoxin reductase are homologous to glutathione reductase with a carboxyl-terminal elongation containing a conserved catalytically active penultimate selenocysteine residue. J. Biol Chem 273 (15): 8581-91.). Revealing the structure in a novel selenoprotein contributes studies in selenoproteins.

Disclosure of the Invention

An objective of the present invention is to isolate an

XIAP-biding protein and a DNA encoding the same. In addition, the present invention aims to isolate a novel protein having a TxR activity derived from human, and a DNA encoding the same.

The present inventors searched for an XIAP-binding protein using the yeast two hybrid system. As a result, a gene encoding an XIAP-binding protein has been successfully isolated from a human placenta cDNA library. A protein encoded by this gene was found to have a TxR activity to complete the present invention. Specifically, the present invention relates to the following proteins, DNAs encoding the same, methods for producing the same, and uses thereof.

(1) A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4.

(2) A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4 in which one or more amino acids are replaced, deleted, added, and/or inserted, having homology of 60% or higher to the amino acid sequence of SEQ ID NO: 2 or 4, and having a thioredoxin reductase activity.

(3) A protein having a thioredoxin reductase activity, encoded by a DNA which hybridizes to the DNA comprising the nucleotide sequence of SEQ ID NO: 1 or 3.

(4) A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4 in which one or more amino acids are replaced, deleted, added, and/or inserted and having an XIAP-binding activity.

(5) A protein encoded by a DNA which hybridizes to the DNA comprising the nucleotide sequence of SEQ ID NO: 1 or 3, and having an XIAP-binding activity.

(6) An antibody biding to the protein of any one of (1) to (5).

(7) A cDNA encoding the protein of any one of (1) to (5).

(8) A cDNA comprising a protein coding region of the nucleotide sequence of SEQ ID NO: 1 or 3.

(9) A vector into which the DNA of (7) or (8) has been inserted.

(10) A transformant carrying the vector of (9).

(11) A method for producing the protein of any one of (1) to (5), the method comprising culturing the transformant of (10).

(12) An antisense DNA against all or a part of the cDNA of (7).

(13) An oligonucleotide comprising a strand of at least 15

nucleotides and hybridizing to the cDNA of (7).

(14) A DNA encoding a protein with a thioredoxin reductase activity and comprising the first exon or the second exon, and the third to the nineteenth exons below:

the first exon, SEQ ID NO: 18;
the second exon, SEQ ID NO: 19;
the third exon, SEQ ID NO: 20;
the forth exon, SEQ ID NO: 21;
the fifth exon, SEQ ID NO: 22;
the sixth exon, SEQ ID NO: 23;
the seventh exon, SEQ ID NO: 24;
the eighth exon, SEQ ID NO: 25;
the ninth exon, SEQ ID NO: 26;
the tenth exon, SEQ ID NO: 27;
the eleventh exon, SEQ ID NO: 28;
the twelfth exon, SEQ ID NO: 29;
the thirteenth exon, SEQ ID NO: 30;
the fourteenth exon, SEQ ID NO: 31;
the fifteenth exon, SEQ ID NO: 32;
the sixteenth exon, SEQ ID NO: 33;
the seventeenth exon, SEQ ID NO: 34;
the eighteenth exon, SEQ ID NO: 35; and
the nineteenth exon, SEQ ID NO: 36.

(15) The DNA of (14), described by SEQ ID NO: 37.

(16) A DNA hybridizing to the nucleotide sequence of any one of SEQ ID NOs: 18 to 36 or a part thereof, which can hybridize to human chromosome 22q11.2.

(17) A DNA which can hybridize to all or a part of a portion of the nucleotide sequence of SEQ ID NO: 37, the portion non-overlapping with the nucleotide sequences of SEQ ID NOs: 18 to 36.

(18) A method for screening a compound having an activity of inhibiting a binding of XIAP with the binding factor, the method comprising the steps of:

(a) contacting simultaneously a candidate substance as a subject for screening, and XIAP with the protein of (2), or

(a)' contacting a candidate substance as a subject for screening with

XIAP, and then, further contacting with the protein of (2),
(b) determining the amount of the protein of (2) which binds and/or does not bind to XIAP, and
(c) selecting a compound which inhibits binding of XIAP with the protein of (2).

(19) A method for screening a compound having an activity of promoting or inhibiting an enzyme activity of thioredoxin reductase II, the method comprising the steps of:
(a) contacting a candidate substance as a subject for screening with the protein of any one of (1) to (3),
(b) observing the change in a thioredoxin reductase activity of the protein of any one of (1) to (3), and
(c) selecting a compound which promotes or inhibits an enzyme activity of thioredoxin reductase II.

SEQ ID NOs: 2 and 4 show amino acid sequences for a novel protein TxRIIα and protein TxRIIβ, respectively, which have been obtained by the present inventors, and SEQ ID NOs: 1 and 3, respectively, show nucleotide sequences of cDNA encoding the same. In the following specification, TxRIIs is used as a term simultaneously containing both TxRIIα and TxRIIβ. These amino acid sequences were deduced based on novel genes structures of which were determined by screening based on a human placenta cDNA library by applying the two hybrid system. The two hybrid method is for confirming interaction among proteins with high sensitivity. The principle is the method for screening a combination of interacting proteins using the expression of a marker gene as an index, as described in Examples. The present inventors applied this method for searching for a substance having an avidity to XIAP to discover a novel factor and reveal the structure.

A location of a gene encoding TxRIIs provided by the present invention was confirmed to be 22q11.2 on chromosomes. Both TxRIIs are present in 70 kbp in this region, by separating into 19 exons. The genes were mapped on chromosomes by database searching, and the presence of genes for proteins having TxR activity in this location was not known at all. TxRIIα and TxRIIβ were determined to be alternative splicing forms of TxRII because they comprised the

identical structure in the second and the following exons. Specifically, the first exon of TxRIIα is Exon 1 below (SEQ ID NO: 18), and the first exon of TxRIIβ is Exon 2 below (SEQ ID NO: 19). The second and the following exons of the both, from Exon 3 (SEQ ID NO: 20) to Exon 19 (SEQ ID NO: 36), are identical.

Interestingly, causative genes of, for example, Di George syndrome, and neurofibromatosis, are mapped close to these TxRII genes, and the possibility of involvement of TxRIIs discovered by us in some inherited disease can not be denied. More importantly, the exon 1 of TxRIIα is overlapped with a promoter region of catechol-o-methyltransferase (EC 2.1.1.6, abbreviated to COMT, hereafter). COMT was also mapped at 22q11.1 11.2 on chromosomes and the direction of transcription was reverse against the TxR II. Namely, it was suggested that, when transcribed, TxR IIα possibly inhibited the expression of COMT by acting on mRNA of COMT in an antisense manner. This may be a cause of schizophrenia and Parkinson's disease. These facts suggest that transcription of COMT can be efficiently inhibited by overexpressing the sense strand DNA of exon 1 in TxRIIα or administering an antisense oligonucleotide or a sense nucleic acid analogue.

Information on the locations of the exons and introns in the genomic DNA provided by the present invention is essential for studying the relationship between these diseases and genetic abnormalities, and may provide a probe for diagnosing these genetic abnormality. Table 1 shows the location for each exon in genome. Each number indicating a location described below is the number when 5' end of the genomic nucleotide sequence in SEQ ID NO: 37 is 1. Based on these information, for example, a DNA hybridizing specifically to each exon can be used as a primer for amplifying an intron part. In contrast, a DNA hybridizing to an intron region except for each exon in the nucleotide sequences of SEQ ID NO: 37 can be used for amplifying an exon by PCR. These primers are essential tools for detecting abnormality in exons and introns. Because inherited diseases may result not only from abnormality in a protein coding region, but also from the abnormality in an intron, leading to the event in which splicing does not occur correctly. Therefore, these

kinds of primers are useful for revealing the inherited diseases. In addition, a DNA which can hybridize to an exon is useful as a probe. Especially, a DNA specifically hybridizing to chromosome 22q11.2 among these DNA is useful as a probe for cloning the genomic DNA of SEQ ID NO: 37 by the present invention. Specifically, by screening a human genomic library as a source with these probes, the genomic DNA of SEQ ID NO: 37 can be isolated. In the case of using as a probe or a primer, the oligonucleotide based on the present invention comprises at least 15 nucleotides to achieve hybridization under stringent conditions, preferably of 15 to 200 nucleotides, and more preferably of 25 to 100 nucleotides.

Table 1

Exon	Nucleotide No.	The structure of a splicing part 3 side	5' side	SEQ ID NO:
Exon 1	1-103	agcag/GTA		18
Exon 2	9247-9446	ccaag/GTG	CAG/caggtc	19
Exon 3	10706-10774	ggagg/GTA	CAG/ccgccc	20
Exon 4	22205-22261	ccaag/GTA	CAG/gcacc	21
Exon 5	22800-22944	gactg/GTA	CAG/gagga	22
Exon 6	23587-23661	gacag/GTA	CAG/aaaag	23
Exon 7	25961-26039	aagag/GTG	CAG/attct	24
Exon 8	26529-26591	cgcac/GTG	CAG/atcga	25
Exon 9	30358-30428	aaaac/GTA	CAG/gttgg	26
Exon 10	43016-43035	cagct/GTA	CAG/atgtg	27
Exon 11	43954-44045	accag/GTA	CAG/caaat	28
Exon 12	46503-46677	catag/GTA	CAG/gtcga	29
Exon 13	58623-58759	tggag/GTA	AAG/gggcg	30
Exon 14	61367-61462	acaat/GTG	CAG/gttct	31
Exon 15	61813-61905	ttgag/GTG	CAG/gtcta	32
Exon 16	63647-63718	taaag/GTG	CAG/atggt	33
Exon 17	63897-63994	atcaa/GTA	CAG/gtgtg	34
Exon 18	64850-65044	cccag/GTA	CAG/gatgg	35
Exon 19	66277-66566	-		36

The amino acid sequence of SEQ ID NO: 2 showed 55% homology to the known human TxR by searching database, and 38% homology to human glutathione reductase. Especially, in a redox active center, a FAD-binding region, a NADPH-binding region, and a selenocysteine active center, homology was completely conserved. Figure 1 shows alignment of amino acid sequences for TxRIIα and the known TxR. The present inventors named the protein comprising the amino acid sequence of SEQ ID NO: 2 TxRIIα, based on these data. Because an avidity with XIAP is not seen in the known human TxR, the protein of the present invention is novel. Homology between these two amino acid sequences does not reach 60%. Therefore, these two are different proteins, and human TxR does not predict structures and functions of TxRIIα or TxRIIβ.

It has been reported that human thioredoxin reductase reported in 1995 contains a sequence of AUUUA in the untranslated region present at 3' side (abbreviated to 3' UTR hereafter). This AUUUA is considered to contribute instability of mRNA and it has been reported that mRNA is rapidly decomposed by the presence of this sequence in 3' UTR. This kind of sequences has been also reported in cytokines and protooncogenes, and it has been known that these proteins increase at once by a stimulus and disappear. These facts suggest that the previously reported human thioredoxin reductase is transiently transcribed and translated by some stimulus and decomposed immediately after that, and that, thus, the effect is limited to a very temporary one. In contrast, this kind of sequences is not present in 3' UTR of TxRIIs of the present invention, and TxRIIs are considered to be constantly involved in controlling redox *in vivo*. Therefore, inhibitors and promoters for TxRIIs are likely to be completely different from the reported inhibitors of TxR in terms of specificity, inhibitory effects, and as therapeutic agents. Therefore, the knowledge regarding TxRIIs, revealed by the present invention, has an important meaning in the development of drugs involved in redox control *in vivo*.

The proteins of the present invention contain not only those disclosed in SEQ ID NOs: 2 and 4, but also mutants having the physiological activity at the same level. Specifically, the present

invention contains the protein comprising the amino acid sequence of SEQ ID NO: 2 or 4, or a protein having an XIAP-biding activity and comprising the amino acid sequence in which one or more amino acids are replaced, deleted, added, and/or inserted. Alternatively the proteins of the present invention contain the protein comprising the amino acid sequence of SEQ ID NO: 2 or 4, or all proteins comprising the amino acid sequences in which one or more amino acids are replaced, deleted, added and/or inserted, and desirably having 60% or higher homology as a whole to the above amino acid sequence and a TxR activity.

As understood from the amino acid sequence of SEQ ID NO: 2 or 4, TxRIIs of the present invention are a selenoprotein containing selenocysteine in a molecule. On the other hand, the previously reported human TxR has been reported to encode Secys by an amino sequence of Cys-Secys-Gly-stop codon (UAA). Moreover, in bovine TxR, this Cys-Secys-Gly at C terminus is a region essential for the activity expression of TxR. Therefore, in human TxRIIs by the present invention, this region is considered to have an important meaning in the TxR activity expression.

A method for adding mutation in an amino acid sequence while maintaining a physiological activity is known. For example, as a method for preparing a mutant using the random mutation, the chemical mutagenesis method (Myers RM, et al. Methods Enzymol., 1987; 155: 501-527) is known. In this method, a random mutation is introduced into a single-stranded DNA of a target gene by adding a nucleotide modification reagent. Then, a double-stranded DNA is synthesized by using appropriate primers with the obtained single stand DNA as a template by PCR and cloned. A target mutant can be obtained by selecting a clone which provides an expression product having an desired activity from a library of mutants. On the other hand, as a method for preparing a mutant by determining a target nucleotide, a method for introducing the mutation by conducting PCR with a target gene as a template using mutation oligonucleotide primers is known (Ito W. et al., Gene 1991 June 15; 102 (1): 67-70). Mutation in an amino acid sequence occurs not only by an artificial manipulation but also in the natural condition. A mutant of the present invention

includes such a naturally occurring mutant as long as it maintains the TxR activity or the XIAP-binding activity.

As a method for confirming the TxR activity, the following two methods are known for example (Holmgren, A. et al. Methods Enzymol. 252: 199). First, using an appropriate SH indicator, such as 5, 5'-dithiobis (2-nitrobenzoic acid) (DTNB), 5-mercapto-2-nitrobenzoic acid (TNB) produced by the TxR activity is measured with absorbance at 412 nm by a thiol. This reaction is shown as follows:

$$DTNB + NADPH + H^+ \rightarrow 2TNB + NADP^+$$

The other index for the TxR activity is a method called an insulin assay in which an enzyme activity is monitored by tracing a change created by the cleavage of the SS-bond of insulin by reduced form Trx resulted from the TxR activity. As a change which is an index, the decrease of absorbance at 340 nm by oxidation of co-enzyme NADPH, and absorbance at 412 nm of a thiol group resulted from reduction of insulin are used. Production process of reduced form Trx by TxR is as described above.

On the other hand, an XIAP-biding activity functionally equivalent to the binding activity in the natural form TxRIIα or β comprising the amino acid sequence of SEQ ID NO: 2 or 4 can be used. As a method for screening functionally equivalent substances, specifically, for example, the following methods can be used. Specifically, the method is a method for screening a compound having an activity of inhibiting the biding of XIAP with the binding substance and comprising the following processes (a) or (a)', (b), and (c):

(a) contacting simultaneously a candidate substance as a subject for screening, and XIAP with the protein of the present invention, or

(a)' contacting a candidate substance as a subject for screening with XIAP, and then, further contacting with the protein of the present invention,

(b) determining the amount of the protein of the present invention which binds and/or does not bind to XIAP, and

(c) selecting a compound which inhibits binding of XIAP and the protein of the present invention.

More specifically, a method according to the method shown as an inhibitor assay of Example 7-5) can be presented. If a diluted series of a candidate compound is used as a sample and the decreased absorbance is observed dependently on the diluted series, the candidate compound is judged to have a binding inhibitory activity. Alternatively, a combinatorial chemistry can be applied. Specifically, a library of candidate compounds is prepared, and the proteins of the present invention are added thereto with XIAP to monitor XIAP to be bound to the candidate compound to screen an antagonistic inhibitory substance for TxRIIs. On the other hand, a compound which blocks the biding of TxRIIs to XIAP can be screened by using TxRIIs which bind to a candidate compound as an index.

In the screening method by the present invention, any proteins can be used as the above-described protein of the present invention as long as it comprises a biding activity domain with XIAP. Specifically, a protein is not necessarily the complete molecule of the amino acid sequence of SEQ ID NO: 2 or 4. In order to observe a binding of candidate compound or the protein of the present invention, these proteins are modified with an observable molecule. As an observable molecule, for example, radioactive isotopes, fluorescent substances, luminescent substances, and enzymatic active substances can be used. In the case of applying the above combinatorial chemistry, an immobilized library of candidate compounds on a solid phase is useful as isolation of reaction solution, washing, and the following measurement of labels are easily manipulated.

These methods can be used, not only for screening mutants in the present invention, but also, for screening compounds which inhibits the binding of XIAP and the protein of the present invention in general. Because a compound screened by this method can control signal transduction system in which XIAP is involved, the proteins provided by the present invention, an antibody thereof, an analogue thereof and such can be expected to have effects of inhibiting cancer, inducing cell death in virus infected cells through promotion of apoptosis, etc.

In addition, a method for screening a compound having an

activity of promoting or inhibiting the enzyme activity can be provided by using TxRIIs of the present invention. This method comprises the steps of:

(a) contacting a candidate substance as a subject for screening with TxRIIs,

(b) observing the change in the TxR activity of TxRIIs, and

(c) selecting a compound which promotes or inhibits the TxR activity in TxRIIs.

TxRIIs to be used for this screening are not necessarily a complete molecule, and a fragment maintaining an enzyme activity of TxRIIs can be used. The TxR activity can be measured based on a method such as the above method. Because the structure of TxRIIs is different from the known TxRI, a compound which affects one activity does not necessarily affect the other. Therefore, a method for screening a substance which affects an enzyme activity of TxRIIs is an essential technique for identifying inhibitors and activators specific to the enzyme activity of TxRIIs or obtaining a compound which affects TxRI in the same manner as in TxRIIs.

As TxR controls redox *in vivo*, an inhibitor for TxRIIs which can be obtained based on the screening method by the present invention can be expected to be used as an anticancer drug, or a therapeutic agent for autoimmune disorders. For example, an organic gold compound used as a general therapeutic agent for rheumatism, an autoimmune disorder, is considered to have a high inhibitory activity on selenoproteins, especially on TxR. Thus, a compound having an inhibitory effect on TxRII can be expected to have a similar pharmacological activity (Stephan Gromer et al., J. Biol. Chem. Vol. 273, No. 32, 20096-20101, 1998). Moreover, if a pharmacological activity through the inhibition of TxR activity is expected, the method for screening a compound which affects an activity of TxRII, provided by the present invention, is useful because it is necessary to select a compound effective not only to a known TxR but also TxRII.

The proteins of the present invention can be obtained by extracting and purifying from cells expressing TxRIIα or β. Selecting cells which highly express a target protein is advantageous. Because the nucleotide sequence of DNA encoding the target protein

is provided, the method for screening cell lines which highly express the target gene by using a probe based on this sequence is routinely conducted by a person skilled in the art. As shown in Examples, TxRIIs by the present invention are expressed in many cultured cells, these cultured cells can be used as a material. A method for purifying a target protein by combining various extraction methods and protein purification methods from cell culture can be selected by a person skilled in the art from experiences. Specifically, various purification methods, for example, gel filtration, ion exchange chromatography, reversed phase chromatography, immuno affinity chromatography, can be used.

Apart from the purification from these natural materials, the proteins of the present invention can be obtained by the genetic engineering technique. For example, an expression vector is constructed by inserting a translation region to an appropriate vector based on the nucleotide sequence of SEQ ID NO: 1 or 3. Then this expression vector is transfected to an appropriate host to express the target TxRII as a recombinant.

In addition, the present invention provides cDNAs encoding the above proteins of the invention. The DNA comprising the nucleotide sequence of SEQ ID NO: 1 or 3 disclosed in the present invention is novel. Regarding cDNA of the present invention, the target gene can be obtained by screening a cDNA library using a probe designed based on, for example, the nucleotide sequence of SEQ ID NO: 1 or 3. Alternatively, the gene of the present invention can be obtained by synthesizing primers based on the nucleotide sequence of SEQ ID NO: 1 or 3, and conducting PCR using a cDNA library as a template. Probes and primers can be designed and prepared based on the nucleotide sequences of cDNA of the present invention by the methods known to a person skilled in the art. In primers for PCR, sequences close to 5′ end and 3′ end of a fragment to be amplified are selected. Addition of a restriction enzyme recognition site to 5′ side of the primers is convenient for insertion into a vector. Both nucleotide sequences of SEQ ID NOs: 1 and 3 comprise the length of about 2 kbp. A whole region of such a length can be amplified by conducting PCR once using a pair of primers and cDNA as a template. A target gene

can be sensitively detected by confirming an amplification product to be obtained by electrophoresis. An expression vector can be constructed by inserting the amplification product into a vector. A commercially available library used in Examples contains a full length cDNA of TxRIIs by the present invention. Therefore, by conducting PCR using this as a template, the cDNA of the present invention can be easily obtained. Alternatively the cDNA of the present invention can be obtained by conducting RT-PCR based on mRNA in each cell line which shown the expression of TxRIIs. An element of 3'UTR is as important as CDS at the construction of the expression vector for active form of TxRIIs, based on the nucleotide sequences of SEQ ID NO: 1 or 3. Among 3' UTR, the portions corresponding to 1780-1909 of SEQ ID NO: 1 and 1883-2012 of SEQ ID NO: 3 (SEQ ID NO: 5, 130 bp) constitute a common nucleotide sequence. This part is essential for expressing a complete form of TxRIIs containing selenocysteine. UGA which is a stop codon in general, is translated to selenocysteine by the stem loop structure composed of a part corresponding to this region in mRNA. As previously described, selenocysteine is considered to be an amino acid essential for an enzyme activity of TxR. Therefore, into the expression vector of the present invention, an insert should be inserted in the form containing this region. If the TxR activity is not expected to TxRIIs of the present invention, this region is not essential. For example, in the case of aiming the expression of a domain peptide of TxRIIs composed only of a specific region, a target protein can be obtained by inserting only the nucleotide sequence encoding a necessary amino acid sequence in the form able to express. To the domain peptide obtained in this manner, an enzyme activity of TxR can not be expected. However, for example, the domain peptide can be used as an immunogen for preparing an antibody which recognizes TxRIIs by the present invention. Alternatively, a mutant with a binding-activity with XIAP based on the present invention can be prepared by selecting a region serving the biding with XIAP.

The DNA of the present invention contains not only the DNA constituted by the nucleotide sequence of SEQ ID NOs: 1 and 3, but also mutants thereof. Mutants of the DNA based on the present

invention are mainly classified to the following two. Specifically, first, a DNA comprising a nucleotide sequence encoding all proteins comprising mutation in the above amino acid sequence by the present invention is the DNA mutant based on the present invention. More specifically, a DNA encoding all mutants comprising mutation in the amino acid sequence within the range of maintaining an activity as TxRIIs are contained in the DNA of the present invention, regardless of being able to hybridizing to SEQ ID NO: 1 or 3 or not. Because several sequences correspond to codons for one amino acid in general (degeneracy), theoretically an astronomical number can be expected for a nucleotide sequences of DNA encoding a given amino acid sequence. From this reason, the DNA nucleotide sequences of the present invention must be identified regardless of complementarity to a specific sequence.

Second, a DNA which can hybridize to SEQ ID NO: 1 or 3, and encodes a protein having an activity as TxRIIs is included in the DNA of the present invention. Many of sequences which can hybridize to a specific sequence under stringent conditions are thought to have an activity similar to the protein encoded by the specific sequence. A specific example of hybridization conditions is 5xSSC, at 25°C in the absence of formamide, preferably, 6xSSC, at 25°C with 40% formamide, and more preferably, 5xSSC, at 40°C with 50% formamide. An example of washing after hybridization is 2xSSC at 37°C, preferably 1xSSC at 55°C, and more preferably 1xSSC at 60°C.

The nucleotide sequence of DNA of the present invention including mutants can be used for various uses based on the known technologies. Based on the cDNA nucleotide sequence identified in the present invention, an oligonucleotide which specifically hybridizes to this nucleotide sequence can be obtained. An oligonucleotide of the present invention is composed of at least 15 nucleotides in order to archive hybridization under stringent conditions, preferably of 15-200 nucleotides, and more preferably 25-100 nucleotides. Such a nucleotide can be used as a probe and a primer. Based on a given sequence, a person skilled in the art routinely designs a probe specifically hybridizing to the sequence. A nucleotide sequence archiving a specific hybridization is not

necessarily completely complementary on a target nucleotide sequence. Variation of sequences is acceptable as long as it can archive the necessary specificity under stringent conditions. An oligonucleotide comprising a determined nucleotide sequence can be obtained by the chemical synthesis. The oligonucleotide can be used for hybridization assays in various formats by adding an appropriate label to the oligonucleotide. In the case of using as a primer, multiple regions can be set depending on a synthesis principle for a complementary strand. For example, as a primer for PCR, a region determining both 5′ and 3′ sides in the segment which is an object of the synthesis is selected. The oligonucleotide of the present invention can be applied to various complementary strand synthesis reaction, for example, not only basic PCR, but also RT-PCR with RNA as a template, nested PCR which enables a sensitive detection by nesting a amplification region, cDNA synthesis, etc.

For example, as a primer for amplifying cDNA of TxRIIs, or for amplifying 3′UTR, the following nucleotide sequences can be presented. By using a primer for amplifying cDNA of TxRIIs described below, TxRIIs of the present invention can be distinguished from a known TxR and cDNA of the latter can be specifically amplified.

Forward primer for TxRIIα (SEQ ID NO: 13):
5′-ACGATGGCGGCAATGGCGGTG-3′
Forward primer for TxRIIβ (SEQ ID NO: 14):
5′-ACCATGGAGGACCAAGCAGGT-3′
Reverse primer for TxRIIs (SEQ ID NO: 15):
5′-TTACCCTCAGCAGCCTGTCAC-3′
Forward primer for 3′UTR (SEQ ID NO: 16):
5′-GCGCCATCCCTGCAGGCCAGG-3′
Reverse primer for 3′UTR (SEQ ID NO: 17):
5′-CACACTTCAGAAAAAGTACCC-3′

The oligonucleotide based on the present invention can be used as an antisense DNA which inhibits the expression of TxRIIs. There are more than one factors as an inhibitory effect of an antisense nucleic acid on the expression of a target gene (Hirashima and Inoue: "Shin-seikagaku Jikken Koza (New Biochemistry Experiment) 2 Nucleic Acid IV Replication and Expression of a gene", Edited by Japanese

Biochemistry Society, Tokyo-Kagakudojin, pp. 319-347, 1993). The expression of a target gene can be inhibited by any of the effects. In one embodiment, the translation of the gene is effectively inhibited by designing an antisense sequence complementary to non-translation region close to 5′ end of mRNA in the gene. A sequence complementary to a coding region or a non-translation region at 3′ side, however, can be used. A DNA including an antisense sequence of not only a translation region of a gene but also a non-translation region is included in the antisense DNA used in the present invention. An antisense DNA to be used is ligated downstream of an appropriate promoter and preferably a sequence containing a transcription termination signal is ligated to 3′ side thereof. The DNA prepared in this manner can be transfected into cells in which the expression should be inhibited by a known method. A sequence of an antisense DNA is preferably complementary to an endogenous TxRIIs gene contained in cells to be transformed (or a homologous gene) or a part thereof, but is not necessarily completely complementary as long as it is able to effectively inhibit the expression of the gene. A transcribed RNA has preferably 90% complementarity, and the most preferably 95% complementarity on the transcription product of a target gene. To effectively inhibit the expression of the target gene using an antisense sequence, the length of an antisense DNA is at least 15 or more nucleotides, preferably 100 or more nucleotides, and more preferably 500 or more nucleotides. Ordinarily, the length of an antisense RNA to be used is shorter than 5 kb, and preferably shorter than 2.5 kb. The expression of an endogenous gene can be inhibited by using a DNA encoding a ribozyme.

The present invention provides an antibody which recognizes the protein based on the present invention. An antibody of the present invention can be prepared by immunizing the protein obtained in the above manner or a fragment thereof through a known method. In immunization, adjuvant, such as FCA, is mixed with an immunogen and subcutaneously immunized to an animal to be immunized by an appropriate immunization schedule. High immune stimulation can be expected by selecting an animal to be immunized, in which the structure of TxR is as different from that of human as possible. An

antibody can be prepared not only as a polyclonal antibody purified from serum of the immunized animal, but also as a monoclonal antibody which can be obtained by cloning antibody-producing cells. The method for collecting antibody-producing cells of an immunized animal and establishing cell lines which produce monoclonal antibodies by fusing the cell lines with cultured cell lines enabling cloning is obvious to a person skilled in the art. The antibody obtained in this manner can be used for immunologically detecting and purifying TxR by the present invention.

Moreover a gene in variable region of an antibody contained in antibody-producing cells which recognizes TxRIIs derived from animals of different species can be used for humanization. Specifically, for example, a chimeric antibody which comprises a constant region of a human antibody in the antibody variable region of a mouse can be created by gene recombination. A method for obtaining a so-called humanized antibody in which a hypervariable region is solely inserted into a framework of a human antibody is known. These humanized antibodies can be safely and effectively used *in vivo* because an immunological reaction is difficult to occur in the case of administering to human.

Brief Description of the Drawings

Figure 1 shows the alignment of amino acid sequences for TxRIIα of the present invention and the known TxR.

Figure 2 is a photograph showing the result of detecting TxRIIs in each cultured cell line by Western blot method using an antiserum of mouse anti-TxRIIα.

Figure 3 shows the TxR activity measured by the DTNB assay in the TxRIIα recombinants fused with each tag. The vertical and horizontal axes indicate absorbance at 412 nm and reaction time, respectively.

Figure 4 shows the TxR activity measured by insulin assay in the TxRIIα recombinants fused with each tag. The vertical and horizontal axes indicate change of absorbance at 340 nm and reaction time, respectively.

Figure 5 shows effects of the TxR activity inhibitor on the TxR

activity of the flag-tag fused TxRIIα protein, measured by the DTNB assay. As a TxR activity inhibitor; 1-chloro-2, 4-dinitrobenzene (CDNB) and 13-cis-retinoic acid are used. The vertical and horizontal axes indicate absorbance at 412 nm and reaction time, respectively.

Best Mode for Carrying Out the Invention

The present invention is illustrated in detail below based on the Examples.

All techniques used in the present invention followed J. Sambrook, E. F. Fritsch & T. Maniatis (1989) Molecular Cloning, a laboratory manual, second edition, Cold Spring Harbor Laboratory Press.

1. Cloning of XIAP by PCR

1-1) Preparation of primers

The following two primers were synthesized to isolate the full length human XIAP gene by PCR.

· 5′ primer (XIAP2486 (32mer))

5′-GCG GGA TCC ATG ACT TTT AAC AGT TTT GAA GG-3′

* 3 bases (GCG) at 5′end are for conveniently conducting the restriction enzyme treatment.

(GGATCC) from the 4th to the 9th bases at 5′ end is a restriction enzyme BamH I site.

· 3′ primer (XIAP 2482 (32 mer))

5′-GCG CTC GAG CTA CTA TAG AGT TAG ATT AAG AC-3′

*3 bases (GCG) at 5′end are for conveniently conducting the restriction enzyme treatment.

(CTCGAG) from the 4th base to the 9th base at 5′ end is a restriction enzyme Xho I site.

1-2) PCR

Using the cDNA derived from human T-cell-derived Jurkat cells as a template DNA, the full length human XIAP gene was amplified by PCR. PCR was conducted with GeneAmp PCR System 2400 (PERKINELMER) by the following program.

a) 94°C for 5 min
b) 1 cycle of 94°C for 1 min, 58°C for 3 min, 72°C for 3 min
c) 35 cycles of 94°C for 1 min, 65°C for 1 min, 72°C for 2 min
d) 72°C for 10 min

1-3) Cloning of a PCR product to pAS2-1 vector

i) Purification of a PCR product

The amplified DNA fragment was confirmed by the 1% agarose electrophoresis after PCR. This DNA fragment was treated with restriction enzymes BamH I and Xho I. The DNA fragment treated with restriction enzymes was electrophoresed by the 1% agarose, excised and purified by Glass Matrix method (GeneClean, BIO101).

ii) Preparation of vector

Vector pAS2-1 is a bait vector used in MATCHMAKER Two Hybrid System (a product name) of Clontech, and comprises a multicloning site (MCS) downstream of a sequence encoding GAL4-DNA-BD (a DNA biding domain of GAL4 protein). A bait in the two hybrid system means a vector in the side which expresses a known protein functioning as a probe for searching unknown binding factors. To match translation frames for GAL4-DNA-BD and the PCR product, this MCS was digested with Nde I at the restriction enzyme Nde I site, blunt-ended by the standard method, and self-ligated to obtain the vector pASΔNdeI (+2) in which two frames were slipped. The fragment treated with restriction enzymes BamH I and Sal I was purified in the same manner for a PCR product. The purified product and the fragment of vector pAS2-1ΔNdeI were ligated. The purified PCR product and pAS2-1ΔNdeI were mixed in the molar ratio of 1, and reacted for 1 hour at 16°C with T4 DNA ligase.

iii) Transformation of *E. coli*

A ligation reaction solution was added to *E. coli* strain DH5α made competent by the standard method (Hanahan, D. 1983 Studies on transformation of *Escherichia coli* with plasmids, J. Mol. Biol 166: 557), gently mixed, kept on ice for 30 min, heat-shocked for 90 sec in warm water at 42°C, kept on ice for 2 min again, and cultured with

shaking at 37°C for 1 hour in SOC medium. The product was spread on a LB plate containing 50 μg/ml ampicillin and cultured overnight at 37°C.

iv) Collection of DNA by the alkaline-SDS method and confirmation of an insert

Colonies were harvested from the plates and cultured in a LB-ampicillin medium at 37°C overnight. From the cultured *E. coli*, plasmid DNA was collected using the alkaline-SDS method. The collected plasmid DNA was cleaved by an appropriate restriction enzyme and insertion of the target PCR product into the vector was confirmed by the agarose electrophoresis.

v) Confirmation of sequences

The collected DNA was purified by the polyethylene glycol precipitation method and the PCR product in the vector was confirmed by the fluorescence sequencer (PERKINELMER) based on the Sanger method. In this manner, plasmid DNA of pASΔNdeI (+2) -XIAP in which the full length human XIAP gene was inserted into pASΔNdeI (+2) vector was obtained.

2. 2 Hybrid screening

In analyses of intracellular information transduction mechanisms and studies on cellular mechanisms at higher levels, detection of interaction between proteins and identification of known or unknown molecules interacting with a known protein are very important. The two hybrid screening system has been given attention for detecting a interaction between proteins encoded by two genes, or as a method for cloning a molecule interacting a gene product. In this method, each of two gene products is fused to a DNA binding site (GAL4-DNA-BD) and a transcription activation site (GAL4-AD) in a transcription factor, to detect the interaction between two, using a transcription activity as an index. A GAL4-DNA-BD fusion protein and a GAL4-AD fusion protein are simultaneously expressed in a yeast nucleus. When the both interact, HIS3 gene comprising GAL4 promoter upstream and lac Z gene are expected to be transcribed and translated.

Specifically, the yeast can grow in the agar medium without histidine only in the presence of the interaction between the both, and β-galactosidase (abbreviated to β-Gal, hereafter) activity can be detected using X-gal as a substrate. The two hybrid screening system is so advantageous that interaction of two gene products can be judged in a yeast nucleus *in vivo* without purifying the proteins. However, a protein transcribed from the GAL4 promoter without showing interaction can not be screened. Therefore, it is very important to confirm that lac Z gene does not express only with the GAL4-DNA-BD fusion protein, namely, there is no β-Gal activity. For the two hybrid screening, the MATCHMAKER two hybrid system method 2 of CLONTECH was used and all experimental methods followed this protocol.

2-1) Purification of a library DNA for pray

Human Placenta MATCHMAKER cDNA Library purchased from CLONTECH was used as a library for screening. This library was prepared by pACT2 vector and contains a MCS downstream of a sequence encoding GAL4-AD (an Activation Domain of the GAL4 protein) and a cDNA fragment was inserted into this MCS. In the two hybrid system method, a library predicted to contain unknown binding factors is called a pray. About 20,000 colonies per an LB-ampicillin plate with a diameter of 150 mm were spread and these 100 plates were cultured at 30°C overnight and bacterial cells were cultured in a LB ampicillin liquid medium at 30°C for 4 hours. Plasmid DNA was collected from the harvested *E. coli* cells by the polyethylene glycol precipitation method and purified.

2-2) Confirmation of expression of a fusion protein and the absence of β-Gal activity

Yeast was transformed by the constructed pASΔNdeI (2+)-XIAP, and expression of XIAP as the GAL4-DNA-BA fusion protein, and an activation of GAL4 promoter solely by the GAL4-DNA-BD fused XIAP (bait) but no-expression of lac Z gene were confirmed.

Yeast Y 190 made competent by the lithium acetate method (Gietz, D., Jean A., Woods, R. A., & Schiestl, R. H. 1992, Improved method

for high efficiency transformation of intact yeast cells. Nucleic Acid Res. 20: 1425) was transformed by using plasmid DNA of pASΔNdeI (+2)-XIAP. Colonies obtained by transformation were cultured in the SD/-Trp liquid medium at 30°C for 3 days. After the culture, yeast cells were harvested by centrifugation, and proteins were extracted from yeast by the standard method (Printen, J. A. & Sprague, G. F., Jr. (1994) Protein interactions in the yeast pheromone response pathway: Step 5 interacts with all members of the MAP kinase cascade. Genetics 138: 609-619), using the urea/SDS protein extraction buffer. After electrophoresis of proteins by SDS-PAGE, the proteins were blotted on the PVDF protein. The expression of the fusion protein of GAL4-DNA-BD and XIAP was confirmed by Western blot using the anti-GAL4 DNA binding domain monoclonal antibody (CLONTECH) and anti-XIAP polyclonal antibody.

A sterile nylon transfer membrane (Hybond-N+, Amersham) was placed on the plate on which yeast transformants in which expression of the fusion protein between GAL4-DNA-BD and XIAP was confirmed were grown. Thus, the colonies were transferred to the membrane. This membrane was immersed in liquid nitrogen for 10 sec, returned to room temperature, placed on a filter paper immersed with the Z-buffer/X-gal solution (100 ml Z-buffer (16.1 g/L Na_2HPO_4-$7H_2O$, 5.50 g/L NaH_2PO_4-H_2O, 0.75 g/L KCl, 0.246 g/L $MgSO_4$-$7H_2O$, adjusted to pH 7.0), 0.27 ml mercaptoethanol, 1.67 ml X-gal solution (20 mg/ml X-gal in DMFA)) with the surface with colonies up, and kept at 30°C for one hour or longer. As a result, the yeast transformants in which the expression of the fusion protein of GAL4-DNA-BD and XIAP was confirmed did not turn blue. Specifically, sole the fusion protein of GAL4-DNA-BD and XIAP did not activate transcription from the GAL4-promoter, confirming that the two hybrid screening system can be used.

2-3) The primary screening

The yeast transformants in which the expression of the fusion protein of GAL4-DNA-BD and XIAP was confirmed were mass-cultured and were made competent by the lithium acetate method. These were transformed by the previously prepared Human Placenta MATCHMAKER

cDNA library. The obtained transformants were streaked on the plates of SD/-Trp/-Leu/-His/+3-AT, and cultured for 7 days at 30°C. By this, only yeast in which bait bound to pray and His3 gene downstream of the GAL4 promoter expressed to become His+ can only grow to form colonies. Independent clones of the library used were 5×10^6 and actually screened ones were $72.5 \times 10^7$7, and thus about 5 times were screened. His+ yeasts in this first screening were 82 clones.

2-4) The second screening; β-gal assay

To confirm that in the clones obtained in the first screening, a bait actually bound to a pray to express a gene downstream of the GAL4 promoter, expression of another lac Z gene located downstream of the GAL4 promoter, specifically β-gal activity, was examined. A nylon transfer membrane was placed on the SD/-Trp/-Leu/-His/+3-AT agar plate, and 82 yeast clones which became His+ in the first screening were cultured and grown on this membrane. Clones having His+ and the β-gal activity were obtained by measuring the β-gal activity by colony lift filter assay. By this second screening, 74 colonies having the β-gal activity were obtained.

2-5) Sequencing of a pray

Plasmid DNA was harvested from yeast and transferred to *E. coli*, to examine DNA sequences inserted into the clones obtained by screening.

The yeast clones having His+ and the β-gal activity were scratched from the plates, and cultured on the SD/-Leu medium overnight. Bacterial cells were collected and treated by following the standard method (Kaiser, P. & Auer, B. (1993) Rapid shuttle plasmid preparation from yeast cells by transfer to *E. coli*. Bio Techniques 14: 552) to collect yeast plasmid DNA.

E. coli HB101 for electroporation, made competent using HEPES-NaOH was electrotransformed with the plasmid DNA collected from yeast. After electroporation, SOC medium warmed at 37°C was added thereto, and the *E. coli* was cultured with shaking at 37°C for 1 hour to recover. The *E. coli* was spread on the -Leu plate (M9 plate

containing 50 μg/ml ampicillin, 40 μg/ml proline, 1 mM thiamine hydrochloride, -Leu dropout solution) and cultured at 37°C overnight. *E. coli* HB101 has LeuB mutation. Therefore, among plasmid DNA obtained from yeast, only library vectors encoding LEU2 gene which can complement leuB mutation can transform the *E. coli* HB101 and form colonies on the plate. From grown *E. coli* HB101, plasmid DNA was extracted by the alkaline-SDS method. *E. coli* DH5α was transformed using the harvested plasmid DNA.

Plasmid DNA of pACT2 vector in *E. coli* DH5α was harvested by the alkaline SDS method, and purified by the polyethylene glycol precipitation method. Based on Sanger method, the nucleotide sequences of the genes in the vectors were confirmed by the florescent sequencer. In this manner, a novel gene X19 was obtained.

2-6) Confirmation by re-transformation

After transforming yeast Y190 with the purified plasmid DNA of pACT2-X19, it was confirmed that sole the fusion protein of the GAL4-AD protein and X19 did not cause transcription from the GAL4 promoter by measuring the β-gal activity. By measuring the β-gal activity in Y190 transformed by pASΔNdeI (+2) -XIAP and pACT2-X19, and measuring the β-gal activity in Y190 transformed by pAS-X19 and pACT-XIAP, transcription from the GAL4 promoter, namely, the binding of XIAP and X19 in the yeast nucleus was confirmed.

3. X19 amino acid sequence homology search

Amino acid sequence homology search was conducted using www service (http://www.genome.ad.jp) of Human Genome Analysis Center, Medical Science Institute, The university of Tokyo, and of Supercomputer Laboratory at Institute of Chemistry, Kyoto University to predict the functions of X19 from the amino acid sequence.

3-1) Sequence homology search program BLAST

Using the non-redundant amino acid sequence data base nr-aa, sequences homologous to amino acid sequence of X19 were searched (blastp search). As a result, X19 was a novel gene having 55% homology to human thioredoxin reductase and 38% homology to human

glutathione reductase. Moreover, functional regions (a redox active center, a FAD-biding region, a NADPH-binding region, a selenocysteine active center) reported in human thioredoxin reductase were completely conserved in the homologous manner in X19 (Figure 1, SEQ ID NO: 1). Therefore, we named X19 human thioredoxin reductase II (TxRII).

4. Obtaining the full length TxRII cDNA

4-1) Obtaining a full length cDNA by colony hybridization

From Human Placenta MATCHMAKER cDNA library, a full length TxRII cDNA was obtained by colony hybridization. For screening, a DNA fragment was amplified by PCR from a partial sequence of the sequenced TxRII and used as a probe.

i) Preparation of a membrane for colony hybridization

Human Placenta MATCHMAKER cDNA library was diluted and spread on a LB (ampicillin) plate with a diameter of 150 mm, on which 4 X 10^4 or more colonies can grow per plate. These 12 plates were prepared and cultured at 30°C overnight. The colonies were transferred to a membrane for hybridization, and the membrane for colony hybridization was prepared by following the standard method.

ii) Preparation of a probe

About 500 bp DNA fragment at N-terminal side was obtained using the following primers by PCR with the cDNA of TxRII as a template.

TxRII-sF3 5'-TAT GAT CTC CTG GTG GTC-3'

TxRII-sR2 5'-GTC ATC ACT TGT GAT TCC-3'

The amplified DNA fragment was separated by the 1% agarose gel electrophoresis, and purified by the glass matrix method. From the purified DNA fragment, a [^{32}P] labeled probe was prepared using the DNA random labeling kit (rediprime DNA labelling system, Amersham) and [α-^{32}P] deoxy-CTP (ICN), and purified by spin column (ProbeQuant G-50 Micro Column, Pharmacia).

iii) Hybridization

Hybridization was conducted using a hybridization bottle and

a hybridization oven (TAITEC). The membrane crosslinked with DNA was pre-hybridized in hybridization buffer (10% PEG6000, 1.5% SSPE, 7% SDS) at 65°C for 1 hour. The [^{32}P] labeled probe was boiled, immediately cooled, and diluted with hybridization buffer warmed at 65°C and the solution used for prehybridization was replaced by the hybridization buffer. Hybridization was conducted at 65°C overnight.

iv) Washing and autoradiography

Hybridization buffer was washed with washing solution of 0.1xSSC, 0.1% SDS, and the level of washing was appropriately confirmed by a survey meter. Washing solution was replaced several times until a count of washing solution was completely absent, and then the membrane was loaded on the film to detect positive colonies by autoradiography.

v) Isolation of positive colonies

Positive colonies were isolated by a Pasteur pipet, diluted by the different dilution ratios, spread on a LB (ampicillin) plate of 100 mm diameter and cultured at 30°C overnight. Hybridization was conduced by the same manner and single positive colony was obtained. From this, plasmid DNA was harvested and the DNA sequence was determined. SEQ ID NO: 1 shows the nucleotide sequence of TxRII α cDNA determined in this manner.

4-2) Obtaining a full length cDNA by PCR cloning

From Human Placenta MATCHMAKER cDNA library used in the two hybrid system, TxRII gene was attempted to obtain by PCR by combining TxRII specific primers and library vector specific primers. Sequences of used primers were set as follows based on the nucleotide sequences of the clones obtained by colony hybridization.

TxRII specific primer 1

5′-ACA GCT TCT GCC ATC TTC CTC-3′

TxRII specific primer 2

5′-AGA AGG TTC CAC GTA GTC CAC-3′

Library vector specific primer

5′-CCA TAC GAT GTT CCA GAT TAC-3′

PCR was conducted by the combination of TxRII specific primer 1 and the library vector specific primer in the following program, using GeneAmp PCR System 2400 (PERKINELMER).

a) 94°C, 5 min

b) 35 cycles of 94°C 30 s, 56°C 30 s, 72°C 1 min and 30 s,

d) 72°C 10 min.

A PCR product was electrophoresed by the 1% agarose gel, excised, and purified to be used as a template for the following PCR. The second PCR was conducted using the combination of the TxRII specific primer 2 and the library vector specific primer by the following program.

a) 94°C, 5 min

b) 35 cycles of 94°C 30 s, 56°C 30 s, 72°C 1 min and 30 s,

d) 72°C 10 min.

The PCR product was electrophoresed by the 1% agarose gel, excised, purified, and cloned by using Topo TA cloning Kit (Invitrogen) and DNA sequence of the PCR product was sequenced. As a result, cDNA containing 5'-non amino acid translation region of about 180 bp was obtained and the first methionine (Met) was judged as the first Met due to the presence of Kozak consensus immediately before the methionine. The sequence at N-terminal side, however, was different from that obtained by the yeast two hybrid method. Because the sequence of the second exon and following sequence in this gene was identical to that in TxRII, the gene was decided to be an alternative splicing form of TxRII. The gene obtained by yeast two hybrid method, and the alternative splicing form were designated TxRIIα and TxRIIβ, respectively. The second exon and the following part in TxRIIβ is identical to that in TxRIIα(SEQ ID NO: 3).

In addition, based on the cDNA nucleotide sequence of TxRIIs, known genomic nucleotide sequences were searched, and the cDNA nucleotide sequence of TxRIIs was mapped on 22q11.2. The genes encoding TxRIIs were present in 70 kbp in this region while separating into 18 exons. The presence of a gene encoding a protein having the binding activity with XIAP or the TxR activity was not predicted in this region.

5. Preparation of anti-TxRII antibody

In order to prepare an antibody against human TxRII proteins, a fusion protein with glutathion-S-transferase (GST) protein was purified as an immunogen, and anti-TxRII mouse antiserum was harvested by immunizing a mouse.

5-1) Expression of the GST-TxRIIα fusion protein

The TxRIIα fragment was re-cloned to pGEX vector (Pharmacia) from pACT2-TxRIIα to construct pGEX-TxRIIα. *E. coli* (DH5α) transformed with this pGEX-TxRIIα was cultured in a LB-ampicillin medium at 37°C overnight. This cultured medium was added to a fresh LB-ampicillin medium at 100X dilution, and cultured at 37°C. When the turbidity of the culture medium reached about 0.6, IPTG (isopropyl-β-D(-)-thiogalactopyranoside) was added thereto at the final concentration of 0.5 mM to express the GST-TxRIIα fusion protein, and cultured at 37°C for further 4 hours. The bacterial cells were harvested by centrifugation after the culture.

The collected bacterial cells were well-suspended in ice-cooled PBS containing 1% Tween -20, and completely crushed by ultrasonication. The crushed solution was centrifuged and the supernatant was passed through a GSH-sepharose 4B column (Pharmacia) to adsorb a GST fusion protein on the column. The column was washed well with WE buffer (10 mM β-mercaptoethanol, 2 mM $MgCl_2$, 20 mM Tris-HCl, (pH7.5)), and the GST-TxRIIα fusion protein was eluted using G buffer (10 mM GSH, 50 mM Tris-HCl, pH 9.6). The eluate was concentrated by 50% glycerol/PBS and the buffer was replaced.

5-2) Immunization of the GST-TxRIIα fusion protein into a mouse, collecting blood, and confirmation of reactivity

The purified GST-TxRIIα fusion protein and Freund's complete adjuvant were emulsified, and intraperitoneally injected into a mouse. This manipulation was repeated once a week for 5 weeks, and blood was collected from the mouse to collect serum containing the anti-TxRII antibody. The immunogen, TxRII overexpressed in mammalian cells, and the reactivity in various cultured cells were confirmed by the Western blotting method using this antiserum.

6. Western blotting method (Figure 2)

Soluble proteins were prepared from cultured cells, and protein concentration was measured by following the standard method (M. M. Bradford, Anal. Biochem. 72, 248, 1976), and SDS-PAGE was conducted with 40 μg of protein per lane. This was immunodetected with anti-TxRII antiserum and the presence of TxRII protein present in each cultured cell line was confirmed. As a result, the expression of TxRII was confirmed in each type of cultured cells. In Figure 2, TxRIIα was the band at around 70 kDa, and TxRIIβ was the band at around 55 kDa. The expression of TxRIIβ was not confirmed in mouse or rat cultured cells. The following 11 cell lines were used as samples.

Raji human Burkitt's lymphoma-derived cell line
Jurkat human T cell acute lymphoblastic leukemia-derived cell line
HL60 human acute promyelocytic leukemia-derived cell line
U937 human histiocytic lymphoma-derived cell line
ZR75-1 human epidermic breast cancer-derived cell line
HepG 2 human protopathic hepatoblastoma-derived cell line
HeLa human uterine cervix cancer-derived cell line
A 431 human vulva squamous cell carcinoma-derived cell line
MRC-5 human-derived normal fibroblast cell line
NIH/3T3 mouse fetus-derived normal fibroblast cell line
Rat-1 rat fetus-derived normal fibroblast cell line

7. Purification and activity measurement of the recombinant TxRII α protein

7-1) Preparation of histidine tag fused TxRIIα protein

To pcDNAHis, a mammalian cell expression vector, was sub-cloned a full length TxRIIα gene containing 3'UTR (SEQ ID NO: 1). By transfecting this plasmid DNA to a mammalian cells, TxRIIα protein in which a histidine tag is added at N-terminal side is overexpressed in the cells. The plasmid DNA was transfected to 293T cells by the lipofection method according to the standard method. The cells were harvested 48 hours after the transfection, and the target protein

was purified by using the kit for purifying a histidine-tag fusion protein.

7-2) Purification of flag-tag fused TxRIIα protein

To pcDNAFlag, a mammalian cell expression vector, the full length gene of TxRIIα containing 3'UTR was sub-cloned. By transfecting this plasmid DNA into mammalian cells, selenocysteine was inserted into a protein, and only a protein in which flag-tag was added at C-terminal side of TxRIIα can be collected with the anti-Flag antibody affinity column.

According to the standard method, using the lipofection method, the plasmid DNA was transfected to 293T cells. The cells were collected 48 hours after the transfection, and the cell extract solution was passed through the anti-Flag antibody affinity column to collect the flag-tag fused TxRIIα protein using a peptide of Flag.

7-3) Purification of the MYC-tag fused TxRIIα protein

To pCMVmyc, a mammalian cell expression vector, the full length gene of TxRIIα containing 3'UTR was sub-cloned. By transfecting this plasmid DNA into mammalian cells, proteins in which MYC-tag is added at N-terminal side in TxRIIα are overexpressed. By following the standard method, using the lipofection method, the plasmid DNA was transfected to 293T cells. The cells were collected 48 hours after the transfection, Protein A sepharose to which the anti-MYC monoclonal antibody was bound was added to the cell extract solution, and gently stirred at 4°C for 2 hours. By centrifuging, the MYC-tag fused TxRIIα protein binding to protein A sepharose to which the anti-MYC monoclonal antibody bound was precipitated, the supernatant was removed, and the proteins were washed several times with NETN buffer (10 mM Tris-HCl, 1 mM EDTA, 0.5% NP-40, 150 mM NaCl).

7-4) Activity measurement

By following the standard method (Holmgren, A. and Bjornstedt, M. 1995, [21], Thioredoxin and Thioredoxin Reductase Methods in Enzymol 252: 199), an activity of TxR was measured by the DTNB assay, and the insulin assay.

i) DTNB assay

DTNB assay is a method in which TNB caused by the TxR activity from DTNB is measured by the absorbance of a thiol at 412 nm based on the following reaction formula. The purified tag fused TxRIIα protein (1 to 50 μl) was added to the assay buffer 1 to mess up to 1.0 ml. The absorbance at 412 nm was measured at 25°C for 5 min (Figure 3).

DTNB + NADPH + H^+ 2TNB + $NADP^+$

Assay buffer 1:

100 mM potassium phosphate pH 7.0, 10 mM EDTA, 0.25 mM NADPH, 0.2 mg/ml bovine serum albumin (BSA), 1% ethanol, 1 mM DTNB

As a result, all TxRIIα purified by three methods was found to have the activity equivalent to that of control TxR derived from *E. coli*. The reason why the activity of histidine and the MYC-tag fused TxRIIα protein is slightly low is considered that TxRIIα in which selenocysteine was not incorporated at C-terminal side was mixed to inhibit the reaction.

ii) Insulin assay

The purified tag-fused TxRIIα protein (1 to 50 μl) was added to the assay buffer 2 and messed up to 1.0 ml. Oxidation of NADPH was measured by decreased absorbance at 340 nm at 30°C for 5 min (Figure 4). The TxR activity reduces Trx and the reduced form Trx further reduces insulin. At this time, the TxR activity can be measured by the amount of NADPH to be oxidized. The amount of oxidized NADPH was calculated by the following calculation formula.

ΔA340 x 0.5 / 6.2

Assay buffer 2:

50 mM phosphate buffer pH 7.0, 20 mM EDTA, 80 mM insulin, 0.25 mM NADPH, 16 mM *E. coli* Trx-S2

As a result, all TxRIIα purified by three methods was found to have the activity equivalent to that of control TxR derived from *E. coli*. The reason why the activity of histidine and the MYC-tag fused TxRIIα protein is slightly low is considered that TxRIIα in which selenocysteine was not incorporated at C-terminal side was mixed to inhibit the reaction.

7-5) Inhibitor assay

To compare an enzyme activity of the TxRIIs by the present invention, obtained as a recombinant, and an activity of the natural TxR, an effect of an inhibitor was observed. As an inhibitor for the TxR activity, 1-chloro-2, 4-dinitrobenzene (CDNB) and 13-cis-retinoic acid was used. For confirming the TxR activity, the DTNB assay was used.

The diluted series of the inhibitors was prepared with 0.2 ml of HE buffer (100 mM HEPES buffer pH 7.2, 5 mM EDTA). The tag-fused TxRIIα protein was prepared at 3 μM and 0.2 ml thereof was added thereto, then 0.2 ml of HE buffer containing 3 mM NADPH and 30 mM DTNB was added thereto. The reaction system of this solution is composed of 100 mM HEPES buffer pH 7.2, 5 mM EDTA, 1 μM flag-tag fused TxRIIα protein, 1 mM NADPH, and 10 mM DTNB. The amount of reduced insulin was measured by absorbance of a thiol at 412 nm at 25°C for 5min. Figure 5 shows the result.

As a result, the activity of the purified flag-tag fused TxRIIα protein was clarified to be effectively inhibited by CDNB and 13-cis retinoic acid, as previously reported in the references of TxR I. The TxRIIα of the present invention was predicted to express an enzyme activity by the same mechanism as in the known TxR.

Industrial Applicability

Higher animal's TxR was first purified as an enzyme in the 1990's, and the amino acid sequence thereof was reported in 1995. TxR in higher animals was given attention due to the difference in the size and substrate specificity of the proteins from the homologues in lower animals reported previously. The presence of TxRIIs in human, however, was not predicted, and thus the structure and activity of TxRIIs revealed in the present invention is very meaningful. The following is the importance of the present invention in detail.

The present invention provides an important information in screening of anticancer agents. It has been mentioned that TxR is given attention as a target for an anticancer agent. The importance of the present invention is large because it revealed that there are

more than one species of molecules for the target. Specifically, to provide more certain therapeutic effects, an approach for comprehensively controlling the TxR activity including TxRIIs of the present invention is needed. This kind of approach can be possible first by the knowledge of the present invention.

In a cDNA provided by the present invention, there is 3'UTR constituting the stem loop structure essential for translating selenocysteine present close to C-terminus of TxRIIs. This nucleotide sequence supports the expression of the region containing selenocysteine essential for the expression of the TxR activity. The 3'UTR clarified in the present invention is composed of only 130 bp, and the fact that selenocysteine can be translated by such a short sequence is a novel knowledge. Moreover, considering the present invention from the aspect that the XIAP-binding protein was isolated, the protein of the present invention may bind to XIAP serving the control of apoptosis and, thus, may control the functions. The present invention provides a novel technique for promoting apoptosis, through this possibility. Promotion of apoptosis induces the death of abnormal cells, for example, cancer and virus-infected cells, leading to the treatment of the diseases.

CLAIMS

1. A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4.

2. A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4 in which one or more amino acids are replaced, deleted, added, and/or inserted, having homology of 60% or higher to the amino acid sequence of SEQ ID NO: 2 or 4, and having a thioredoxin reductase activity.

3. A protein having a thioredoxin reductase activity, encoded by a DNA which hybridizes to the DNA comprising the nucleotide sequence of SEQ ID NO: 1 or 3.

4. A protein comprising the amino acid sequence of SEQ ID NO: 2 or 4 in which one or more amino acids are replaced, deleted, added, and/or inserted and having an XIAP-binding activity.

5. A protein encoded by a DNA which hybridizes to the DNA comprising the nucleotide sequence of SEQ ID NO: 1 or 3, and having an XIAP-binding activity.

6. An antibody biding to the protein of any one of claims 1 to 5.

7. A cDNA encoding the protein of any one of claims 1 to 5.

8. A cDNA comprising a protein coding region of the nucleotide sequence of SEQ ID NO: 1 or 3.

9. A vector into which the DNA of claim 7 or 8 has been inserted.

10. A transformant carrying the vector of claim 9.

11. A method for producing the protein of any one of claims 1 to 5, the method containing culturing the transformant of claim 10.

12. An antisense DNA against all or a part of the cDNA of claim 7.

13. An oligonucleotide comprising a strand of at least 15 nucleotides and hybridizing to the cDNA of claim 7.

14. A DNA encoding a protein with a thioredoxin reductase activity and comprising the first exon or the second exon, and the third to the nineteenth exons below:

the first exon, SEQ ID NO: 18;

the second exon, SEQ ID NO: 19;

the third exon, SEQ ID NO: 20;
the forth exon, SEQ ID NO: 21;
the fifth exon, SEQ ID NO: 22;
the sixth exon, SEQ ID NO: 23;
the seventh exon, SEQ ID NO: 24;
the eighth exon, SEQ ID NO: 25;
the ninth exon, SEQ ID NO: 26;
the tenth exon, SEQ ID NO: 27;
the eleventh exon, SEQ ID NO: 28;
the twelfth exon, SEQ ID NO: 29;
the thirteenth exon, SEQ ID NO: 30;
the fourteenth exon, SEQ ID NO: 31;
the fifteenth exon, SEQ ID NO: 32;
the sixteenth exon, SEQ ID NO: 33;
the seventeenth exon, SEQ ID NO: 34;
the eighteenth exon, SEQ ID NO: 35; and
the nineteenth exon, SEQ ID NO: 36.

15. The DNA of claim 14, described by SEQ ID NO: 37.

16. A DNA hybridizing to the nucleotide sequence of any one of SEQ ID NOs: 18 to 36 or a part thereof, which can hybridize to human chromosome 22q11.2.

17. A DNA which can hybridize to all or a part of a portion of the nucleotide sequence of SEQ ID NO: 37, the portion non-overlapping with the nucleotide sequences of SEQ ID NOs: 18 to 36.

18. A method for screening a compound having an activity of inhibiting a binding of XIAP with the binding factor, the method comprising the steps of:

(a) contacting simultaneously a candidate substance as a subject for screening, and XIAP with the protein of claim 2, or

(a)' contacting a candidate substance as a subject for screening with XIAP, and then, further contacting with the protein of claim 2,

(b) determining the amount of the protein of claim 2 which binds and/or does not bind to XIAP, and

(c) selecting a compound which inhibits binding of XIAP with the protein of claim 2.

19. A method for screening a compound having an activity of

promoting or inhibiting an enzyme activity of thioredoxin reductase II, the method comprising the steps of:

(a) contacting a candidate substance as a subject for screening with the protein of any one of claims 1 to 3,

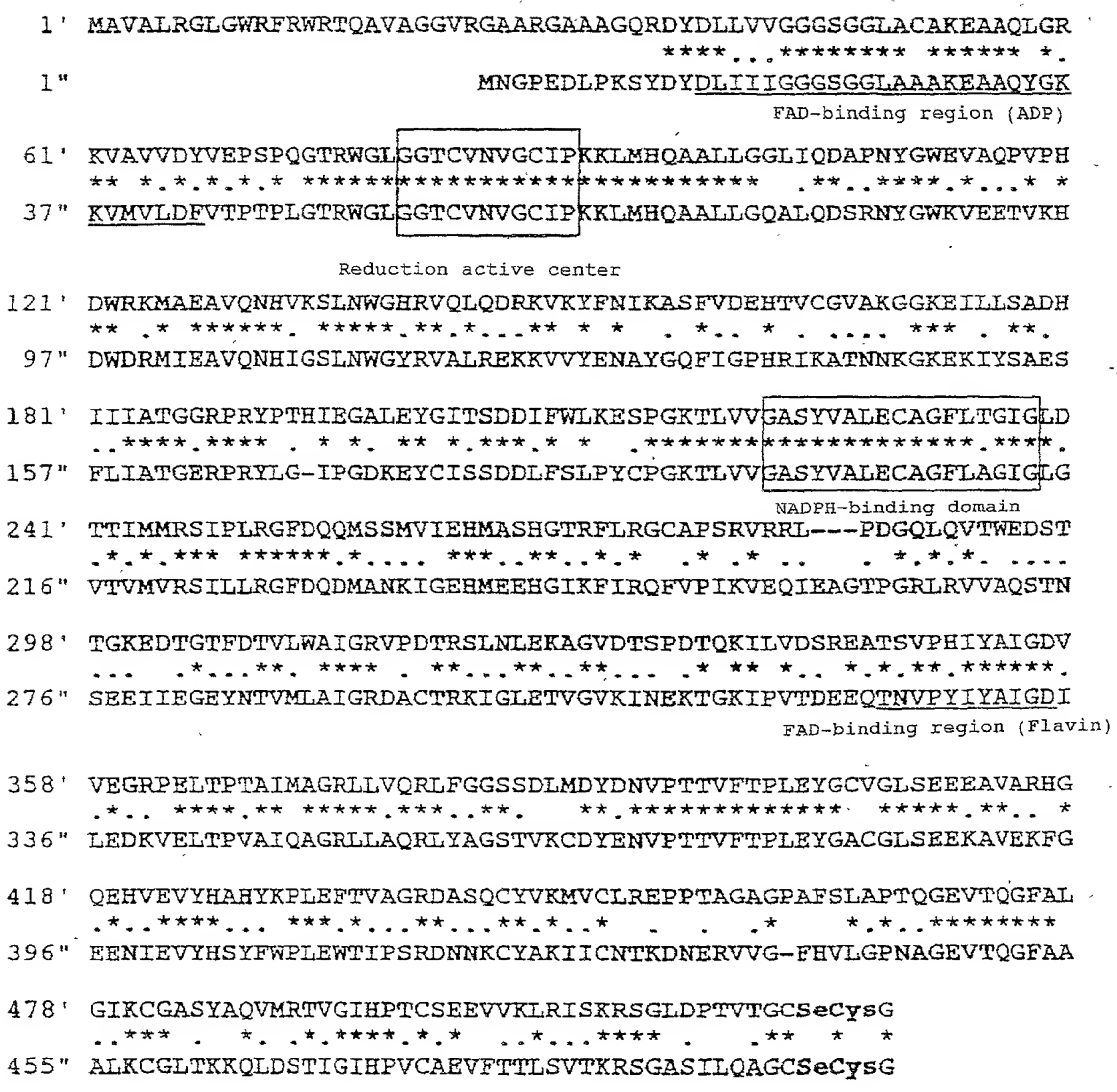
(b) observing the change in a thioredoxin reductase activity of the protein of any one of claims 1 to 3, and

(c) selecting a compound which promotes or inhibits an enzyme activity of thioredoxin reductase II.

ABSTRACT

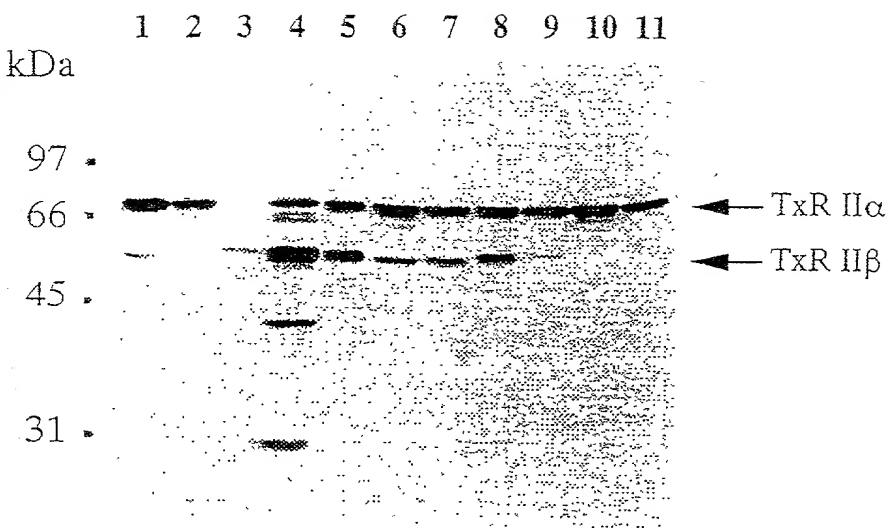
An XIAP-biding protein and cDNA encoding the same were provided. This protein having a thioredoxin reductase activity is named thioredoxin reductase II (TxRII). It is also clarified that TxRII has subfamilies TxRIIα and TxRIIβ by alternative splicing.

Figure 1



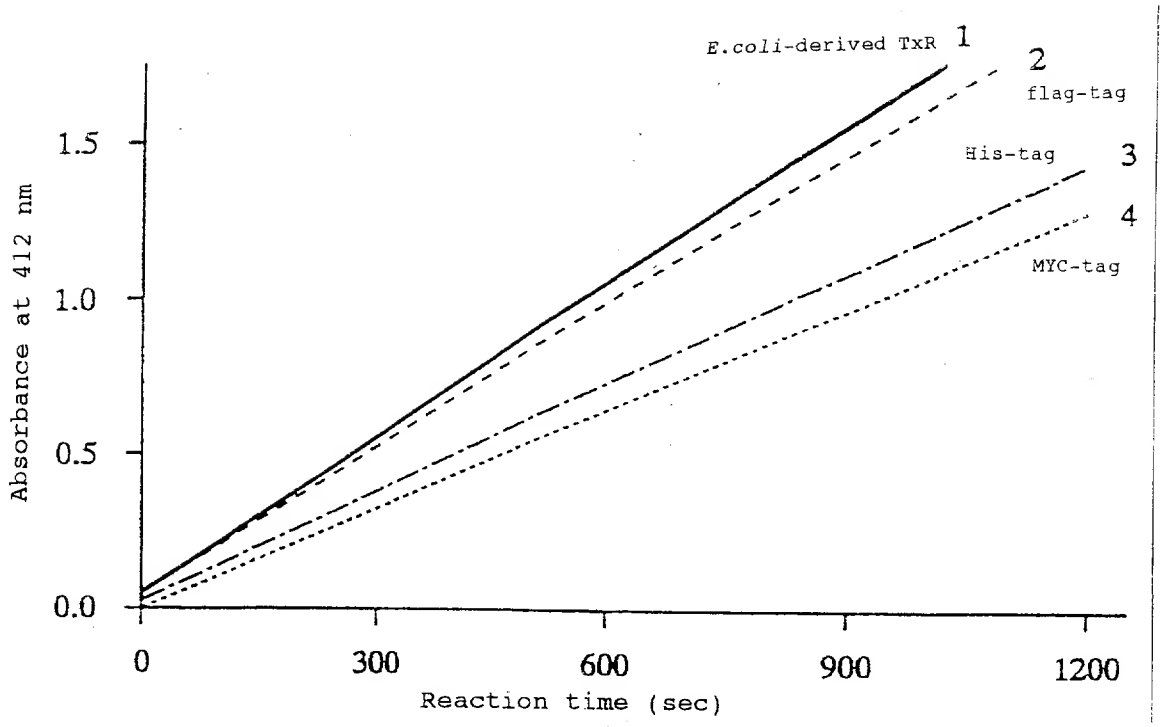
09/830706

Figure 2



1 Raji
2 Jurkat
3 HL60
4 U937
5 ZR75-1
6 HepG 2
7 HeLa
8 A431
9 MRC 5
10 NIH3T3
11 Rat-1

Figure 3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1
2
flag-tag
His-tag
3
4
MYC-tag
Absorbance at 412 nm
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1.0
0.5
0.0
0
300
600
900
1200
Reaction time (sec)

Figure 4

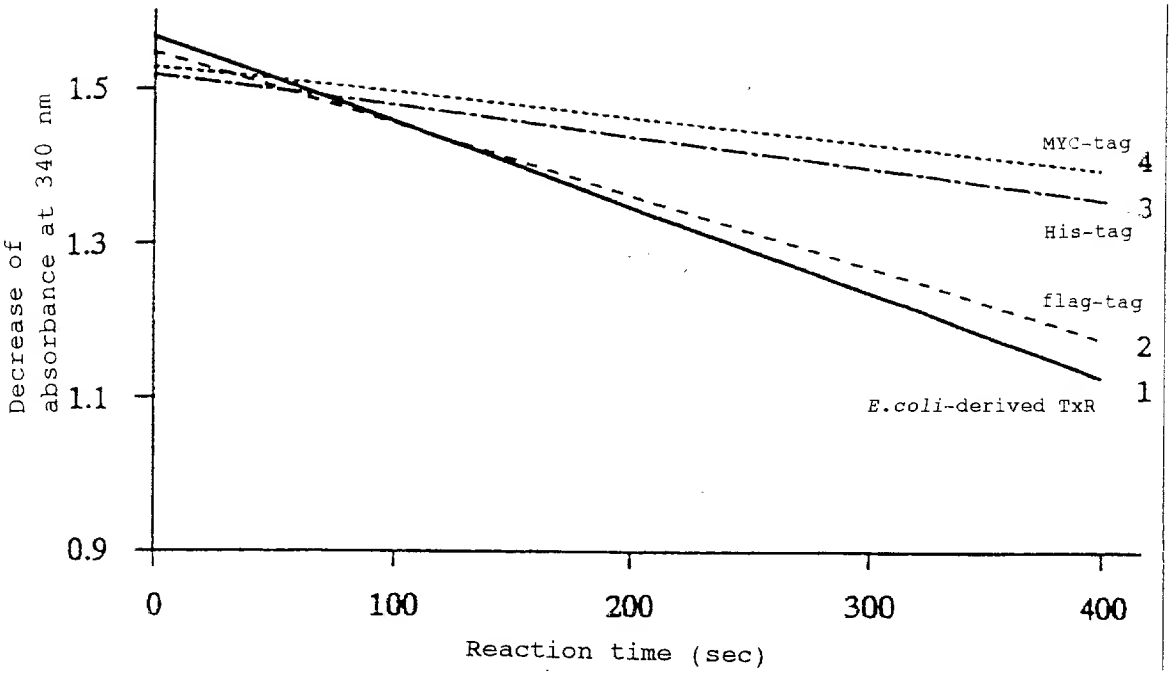
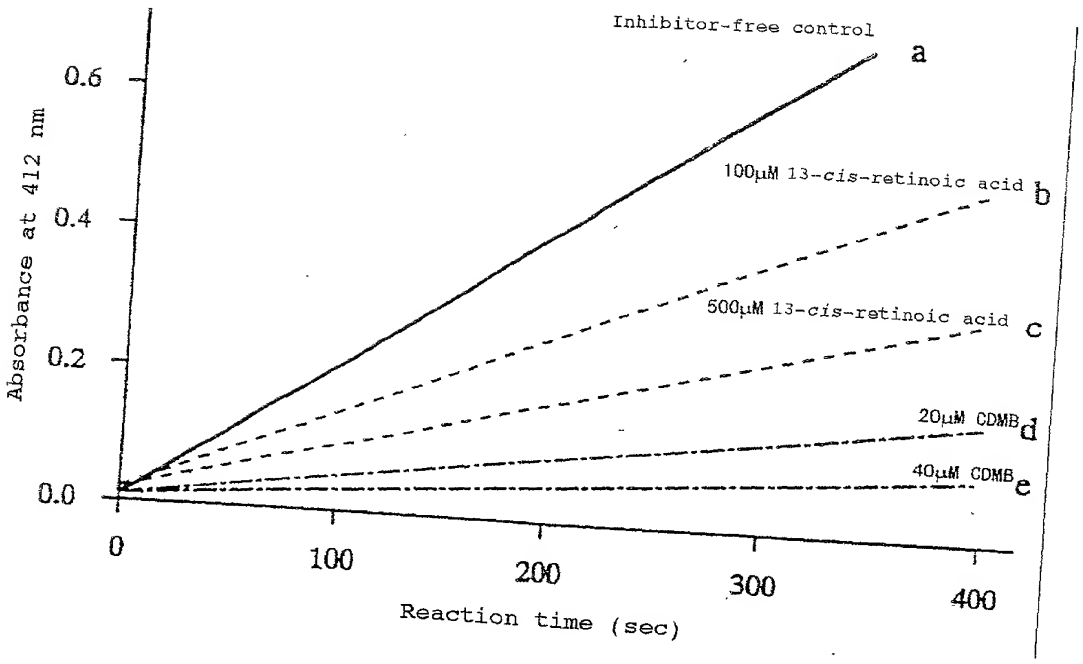

Decrease of absorbance at 340 nm
1.5
1.3
1.1
0.9
0
100
200
300
400
Reaction time (sec)
MYC-tag
4
3
His-tag
flag-tag
2
1
E.coli-derived TxR

Figure 5



DIKE, BRONSTEIN, ROBERTS & CUSHMAN
INTELLECTUAL PROPERTY GROUP OF
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, Massachusetts 02209

Docket No. 55865

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

THIOREDOXIN REDUCTASE II

which is described and claimed in:

☐ the specification attached hereto.

☒ the specification in the U.S. patent application of the same title filed on April 27, 2001, which claims priority from International Application No. PCT/JP99/05983, filed October 28, 1999.

☐ the specification in PCT international application Number_____, filed on _____; and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a). I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign/PCT Applications and Any Priority Claims Under 35 U.S.C. §119:			
Application No.	**Filing Date**	**Country**	**Priority Claimed Under 35 U.S.C. §119?**
JP 10/310422	**October 30, 1998**	**Japan**	☒YES ☐NO
PCT/JP99/05983	**October 28, 1999**	**PCT**	☒YES ☐NO
			☐YES ☐NO

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose material information as defined in 37 CFR §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Prior U.S. Applications or PCT International Applications Designating the U.S-Benefit Under 35 U.S.C. §120					
U.S. Applications			Status (Check One)		
Application Serial No.		U.S. Filing Date	Patented	Pending	Abandoned
PCT Applications Designating the U.S.					
Application No.	Filing Date	U.S. Serial No. Assigned			

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. §119(e))

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Applicant	Provisional Application Number	Filing Date

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) with full powers of association, substitution and revocation to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

David G. Conlin (Reg. No. 27,026)
George W. Neuner (Reg. No. 26,964)
Linda M. Buckley (Reg. No. 31,003)
Christine C. O'Day (Reg No. 38,256)
Peter J. Manus (Reg. No. 26,766)
John B. Alexander (Reg. No. P-48,399)
Cara Z. Lowen (Reg. No. 38,227)
William J. Daley, Jr. (Reg. No. 35,487)
Robert L. Buchanan (Reg. No. 40,927)
Steven M. Jensen (Reg. No. 42,693)
Lisa Hazzard Swiszcz (Reg. No. 44,368)
David A. Tucker (Reg. No. 27,840)
George W. Hartnell, III (Reg. No. 42,639)
Peter F Corless (Reg. No. 33,860)
Stuart L. Gitler (Reg. No. 31,256)
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Peter F. Corless Dike, Bronstein, Roberts & Cushman Intellectual Property Practice Group Edwards & Angell, LLP 130 Water Street Boston, Massachusetts 02109	Peter F. Corless (617) 523-3400

201	FULL NAME OF INVENTOR	LAST NAME **TOJI**	FIRST NAME **Shingo**	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY **Nagano** JPY	STATE OR FOREIGN COUNTRY **Japan**	COUNTRY OF CITIZENSHIP **Japan**
	POST OFFICE ADDRESS	POST OFFICE ADDRESS **c/o Medical & Biological Laboratories Co., Ltd. 1063-103, Aza Ohara, Oaza Terasawaoka, Ina-shi**	CITY **Nagano**	STATE OR COUNTRY AND ZIP CODE **396-0002 JAPAN**
202	FULL NAME OF INVENTOR	LAST NAME **YANO**	FIRST NAME **Minoru**	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY **Nagano** JPY	STATE OR FOREIGN COUNTRY **Japan**	COUNTRY OF CITIZENSHIP **Japan**
	POST OFFICE ADDRESS	POST OFFICE ADDRESS **c/o Medical & Biological Laboratories Co., Ltd. 1063-103, Aza Ohara, Oaza Terasawaoka, Ina-shi**	CITY **Nagano**	STATE OR COUNTRY AND ZIP CODE **396-0002 JAPAN**
203	FULL NAME OF INVENTOR	LAST NAME **TAMAI**	FIRST NAME **Katsuyuki**	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY **Nagano** JPY	STATE OR FOREIGN COUNTRY **Japan**	COUNTRY OF CITIZENSHIP **Japan**
	POST OFFICE ADDRESS	POST OFFICE ADDRESS **c/o Medical & Biological Laboratories Co., Ltd. 1063-103, Aza Ohara, Oaza Terasawaoka, Ina-shi**	CITY **Nagano**	STATE OR COUNTRY AND ZIP CODE **396-0002 JAPAN**
204	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY AND ZIP CODE
205	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY AND ZIP CODE
206	FULL NAME OF INVENTOR	LAST NAME	FIRST NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY AND ZIP CODE

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature of Inventor **201** Shingo Toji	Signature of Inventor **202** Minoru Yano
Shingo TOJI Date: July 2nd 2001	Minoru YANO Date: July 2nd M.Y. 2001
Signature of Inventor **203** Katsuyuki Tamai	Signature of Inventor **204**
Katsuyuki TAMAI Date: July 2nd 2001	Date:
Signature of Inventor **205**	Signature of Inventor **206**
Date:	Date:

PCT09

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RAW SEQUENCE LISTING DATE: 04/22/2002
PATENT APPLICATION: **US/09/830,706B** TIME: 15:01:38

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Output Set: **N:\CRF3\04222002\I830706B.raw**

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   5       YANO, MINORU
   6       TAMAI, KATSUYUKI
   8 <120> TITLE OF INVENTION: THIOREDOXIN REDUCTASE II
  10 <130> FILE REFERENCE: 55865-71965
  12 <140> CURRENT APPLICATION NUMBER: 09/830,706B
C--> 13 <141> CURRENT FILING DATE: 2002-01-29
  15 <150> PRIOR APPLICATION NUMBER: PCT/JP99/05983
  16 <151> PRIOR FILING DATE: 1999-10-28
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  44 cgg acg cag gcc gtg gcg ggc ggg gtg cgg ggc gcg gcg cgg ggc gca   99
  45 Arg Thr Gln Ala Val Ala Gly Gly Val Arg Gly Ala Ala Arg Gly Ala
  46  15                  20                  25                  30
  48 gca gca ggt cag cgg gac tat gat ctc ctg gtg gtc ggc ggg gga tct   147
  49 Ala Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val Val Gly Gly Gly Ser
  50                  35                  40                  45
  52 ggt ggc ctg gct tgt gcc aag gag gcc gcc cag ctg gga agg aag gtg   195
  53 Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln Leu Gly Arg Lys Val
  54              50                  55                  60
  56 gcc gtg gtg gac tac gtg gaa cct tct ccc caa ggc acc cgg tgg ggc   243
  57 Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr Arg Trp Gly
  58          65                  70                  75
  60 ctc ggc ggc acc tgc gtc aac gtg ggc tgc atc ccc aag aag ctg atg   291
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 66  95                  100                 105                 110
 68 ggc tgg gag gtg gcc cag ccc gtg ccg cat gac tgg agg aag atg gca   387
 69 Gly Trp Glu Val Ala Gln Pro Val Pro His Asp Trp Arg Lys Met Ala
 70                  115                 120                 125
 72 gaa gct gtt caa aat cac gtg aaa tcc ttg aac tgg ggc cac cgt gtc   435
 73 Glu Ala Val Gln Asn His Val Lys Ser Leu Asn Trp Gly His Arg Val
 74              130                 135                 140
 76 cag ctt cag gac aga aaa gtc aag tac ttt aac atc aaa gcc agc ttt   483
 77 Gln Leu Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys Ala Ser Phe
 78          145                 150                 155
 80 gtt gac gag cac acg gtt tgc ggc gtt gcc aaa ggt ggg aaa gag att   531
 81 Val Asp Glu His Thr Val Cys Gly Val Ala Lys Gly Gly Lys Glu Ile
 82      160                 165                 170
 84 ctg ctg tca gcc gat cac atc atc att gct act gga ggg cgg ccg aga   579
 85 Leu Leu Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly Arg Pro Arg
 86 175                 180                 185                 190
 88 tac ccc acg cac atc gaa ggt gcc ttg gaa tat gga atc aca agt gat   627
 89 Tyr Pro Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile Thr Ser Asp
 90                  195                 200                 205
 92 gac atc ttc tgg ctg aag gaa tcc cct gga aaa acg ttg gtg gtc ggg   675
 93 Asp Ile Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu Val Val Gly
 94              210                 215                 220
 96 gcc agc tat gtg gcc ctg gag tgt gct ggc ttc ctc acc ggg att ggg   723
 97 Ala Ser Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr Gly Ile Gly
 98          225                 230                 235
100 ctg gac acc acc atc atg atg cgc agc atc ccc ctc cgc ggc ttc gac   771
101 Leu Asp Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg Gly Phe Asp
102      240                 245                 250
104 cag caa atg tcc tcc atg gtc ata gag cac atg gca tct cat ggc acc   819
105 Gln Gln Met Ser Ser Met Val Ile Glu His Met Ala Ser His Gly Thr
106 255                 260                 265                 270
108 cgg ttc ctg agg ggc tgt gcc ccc tcg cgg gtc agg agg ctc cct gat   867
109 Arg Phe Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg Leu Pro Asp
110                 275                 280                 285
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113 Gly Gln Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly Lys Glu Asp
114             290                 295                 300
116 acg ggc acc ttt gac acc gtc ctg tgg gcc ata ggt cga gtc cca gac   963
117 Thr Gly Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg Val Pro Asp
118         305                 310                 315
120 acc aga agt ctg aat ttg gag aag gct ggg gta gat act agc ccc gac   1011
121 Thr Arg Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr Ser Pro Asp
122     320                 325                 330
124 act cag aag atc ctg gtg gac tcc cgg gaa gcc acc tct gtg ccc cac   1059
125 Thr Gln Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser Val Pro His
126 335                 340                 345                 350
128 atc tac gcc att ggt gac gtg gtg gag ggg cgg cct gag ctg aca ccc   1107
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  133 Thr Ala Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu Phe Gly Gly
  134             370                 375                 380
  136 tcc tca gat ctg atg gac tac gac aat gtt ccc acg acc gtc ttc acc   1203
  137 Ser Ser Asp Leu Met Asp Tyr Asp Asn Val Pro Thr Thr Val Phe Thr
  138         385                 390                 395
  140 cca ctg gag tat ggc tgt gtg ggg ctg tcc gag gag gag gca gtg gct   1251
  141 Pro Leu Glu Tyr Gly Cys Val Gly Leu Ser Glu Glu Glu Ala Val Ala
  142     400                 405                 410
  144 cgc cac ggg cag gag cat gtt gag gtc tat cac gcc cat tat aaa cca   1299
  145 Arg His Gly Gln Glu His Val Glu Val Tyr His Ala His Tyr Lys Pro
  146 415                 420                 425                 430
  148 ctg gag ttc acg gtg gct gga cga gat gca tcc cag tgt tat gta aag   1347
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  153 Met Val Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly Leu His Phe
  154             450                 455                 460
  156 ctt ggc ccc aac gca ggc gaa gtt act caa gga ttt gct ctg ggg atc   1443
  157 Leu Gly Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala Leu Gly Ile
  158         465                 470                 475
  160 aag tgt ggg gct tcc tat gcg cag gtg atg cgg acc gtg ggt atc cat   1491
  161 Lys Cys Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val Gly Ile His
  162     480                 485                 490
  164 ccc aca tgc tct gag gag gta gtc aag ctg cgc atc tcc aag cgc tca   1539
  165 Pro Thr Cys Ser Glu Glu Val Val Lys Leu Arg Ile Ser Lys Arg Ser
  166 495                 500                 505                 510
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W--> 169 Gly Leu Asp Pro Thr Val Thr Gly Cys Xaa Gly
  170                 515                 520
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  174 ccaggtttgg ggggcctcaa ccctctcctg gagcgcctgt gagatggtca gcgtggagcg 1712
  176 caagtgctgg acgggtggcc cgtgtgcccc acagggatgg ctcaggggac tgtccacctc 1772
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207 Leu Ala Cys Ala Lys Glu Ala Ala Gln Leu Gly Arg Lys Val Ala Val
208      50                  55                  60
210 Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr Arg Trp Gly Leu Gly
211  65                  70                  75                  80
213 Gly Thr Cys Val Asn Val Gly Cys Ile Pro Lys Lys Leu Met His Gln
214                  85                  90                  95
216 Ala Ala Leu Leu Gly Gly Leu Ile Gln Asp Ala Pro Asn Tyr Gly Trp
217              100                 105                 110
219 Glu Val Ala Gln Pro Val Pro His Asp Trp Arg Lys Met Ala Glu Ala
220          115                 120                 125
222 Val Gln Asn His Val Lys Ser Leu Asn Trp Gly His Arg Val Gln Leu
223      130                 135                 140
225 Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys Ala Ser Phe Val Asp
226 145                 150                 155                 160
228 Glu His Thr Val Cys Gly Val Ala Lys Gly Gly Lys Glu Ile Leu Leu
229                  165                 170                 175
231 Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly Arg Pro Arg Tyr Pro
232              180                 185                 190
234 Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile Thr Ser Asp Asp Ile
235          195                 200                 205
237 Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu Val Val Gly Ala Ser
238      210                 215                 220
240 Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr Gly Ile Gly Leu Asp
241 225                 230                 235                 240
243 Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg Gly Phe Asp Gln Gln
244                  245                 250                 255
246 Met Ser Ser Met Val Ile Glu His Met Ala Ser His Gly Thr Arg Phe
247              260                 265                 270
249 Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg Leu Pro Asp Gly Gln
250          275                 280                 285
252 Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly Lys Glu Asp Thr Gly
253      290                 295                 300
255 Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg Val Pro Asp Thr Arg
256 305                 310                 315                 320
258 Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr Ser Pro Asp Thr Gln
259                  325                 330                 335
261 Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser Val Pro His Ile Tyr
262              340                 345                 350
264 Ala Ile Gly Asp Val Val Glu Gly Arg Pro Glu Leu Thr Pro Thr Ala
265          355                 360                 365
267 Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu Phe Gly Gly Ser Ser
268      370                 375                 380
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271 385                 390                 395                 400
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PATENT APPLICATION: US/09/830,706B TIME: 15:01:38

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277             420                 425                 430
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280         435                 440                 445
282 Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly Leu His Phe Leu Gly
283     450                 455                 460
285 Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala Leu Gly Ile Lys Cys
286 465                 470                 475                 480
288 Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val Gly Ile His Pro Thr
289                 485                 490                 495
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313 gtcccggacc tcaggcccag ttcagtgtac ttcccctctc tacttcctcc ctccagtccc 60
315 ttctccatcc ctccctttt tggctgcccc ttgcctgcct tcctcgccag tagcttgcag 120
317 agtagacacg atgacacctt ttgcaggcta aaaaggctga gagtggcact atgtgcagtg 180
319 agccacc atg gag gac caa gca ggt cag cgg gac tat gat ctc ctg gtg   229
320         Met Glu Asp Gln Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val
321           1               5                  10
323 gtc ggc ggg gga tct ggt ggc ctg gct tgt gcc aag gag gcc gcc cag   277
324 Val Gly Gly Gly Ser Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln
325  15                  20                  25                  30
327 ctg gga agg aag gtg gcc gtg gtg gac tac gtg gaa cct tct ccc caa   325
328 Leu Gly Arg Lys Val Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln
329                  35                  40                  45
331 ggc acc cgg tgg ggc ctc ggc ggc acc tgc gtc aac gtg ggc tgc atc   373
332 Gly Thr Arg Trp Gly Leu Gly Gly Thr Cys Val Asn Val Gly Cys Ile
333              50                  55                  60
335 ccc aag aag ctg atg cac cag gcg gca ctg ctg gga ggc ctg atc caa   421
336 Pro Lys Lys Leu Met His Gln Ala Ala Leu Leu Gly Gly Leu Ile Gln
337          65                  70                  75
339 gat gcc ccc aac tat ggc tgg gag gtg gcc cag ccc gtg ccg cat gac   469
340 Asp Ala Pro Asn Tyr Gly Trp Glu Val Ala Gln Pro Val Pro His Asp
341      80                  85                  90
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RAW SEQUENCE LISTING ERROR SUMMARY DATE: 04/22/2002
PATENT APPLICATION: US/09/830,706B TIME: 15:01:39

Input Set : A:\55865sequence.txt
Output Set: N:\CRF3\04222002\I830706B.raw

Please Note:
Use of n and/or Xaa have been detected in the Sequence Listing. Please review the Sequence Listing to ensure that a corresponding explanation is presented in the <220> to <223> fields of each sequence which presents at least one n or Xaa.

Seq#:1; Xaa Pos. 520
Seq#:2; Xaa Pos. 520
Seq#:3; Xaa Pos. 493
Seq#:4; Xaa Pos. 493
Seq#:37; N Pos. 31417
Seq#:38; Xaa Pos. 498

VERIFICATION SUMMARY DATE: 04/22/2002
PATENT APPLICATION: **US/09/830,706B** TIME: 15:01:39

Input Set : **A:\55865sequence.txt**
Output Set: **N:\CRF3\04222002\I830706B.raw**

L:13 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:169 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:1 after pos.:1592
L:294 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:2 after pos.:512
L:440 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:3 after pos.:1669
L:559 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:4 after pos.:480
L:2002 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:37 after pos.:31380
L:3281 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:38 after pos.:496

SEQ ID NO: 1

PCT09

RAW SEQUENCE LISTING DATE: 11/14/2001
PATENT APPLICATION: US/09/830,706 TIME: 14:12:30

Input Set : A:\55871965.app
Output Set: N:\CRF3\11142001\I830706.raw

ENTERED

p.5

```
 4 <110> APPLICANT: TOJI, SHINGO
 5       YANO, MINORU
 6       TAMAI, KATSUYUKI
 8 <120> TITLE OF INVENTION: THIOREDOXIN REDUCTASE II
10 <130> FILE REFERENCE: 55865-71965
12 <140> CURRENT APPLICATION NUMBER: 09/830,706
13 <141> CURRENT FILING DATE: 2001-04-27
15 <150> PRIOR APPLICATION NUMBER: PCT/JP99/05983
16 <151> PRIOR FILING DATE: 1999-10-28
18 <150> PRIOR APPLICATION NUMBER: JP 1998-310422
19 <151> PRIOR FILING DATE: 1998-10-30
21 <160> NUMBER OF SEQ ID NOS: 38
23 <170> SOFTWARE: PatentIn Ver. 2.1
25 <210> SEQ ID NO: 1
26 <211> LENGTH: 1959
27 <212> TYPE: DNA
28 <213> ORGANISM: Homo sapiens
30 <220> FEATURE:
31 <221> NAME/KEY: CDS
32 <222> LOCATION: (10)..(1572)
34 <220> FEATURE:
35 <221> NAME/KEY: MOD_RES
36 <222> LOCATION: (520)
37 <223> OTHER INFORMATION: Selenocysteine
39 <400> SEQUENCE: 1
40 atggcggca atg gcg gtg gcg ctg cgg gga tta gga ggg cgc ttc cgg tgg 51
41           Met Ala Val Ala Leu Arg Gly Leu Gly Gly Arg Phe Arg Trp
42             1               5                  10
44 cgg acg cag gcc gtg gcg ggc ggg gtg cgg ggc gcg gcg cgg ggc gca   99
45 Arg Thr Gln Ala Val Ala Gly Gly Val Arg Gly Ala Ala Arg Gly Ala
46  15                  20                  25                  30
48 gca gca ggt cag cgg gac tat gat ctc ctg gtg gtc ggc ggg gga tct   147
49 Ala Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val Val Gly Gly Gly Ser
50                  35                  40                  45
52 ggt ggc ctg gct tgt gcc aag gag gcc gcc cag ctg gga agg aag gtg   195
53 Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln Leu Gly Arg Lys Val
54              50                  55                  60
56 gcc gtg gtg gac tac gtg gaa cct tct ccc caa ggc acc cgg tgg ggc   243
57 Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr Arg Trp Gly
58          65                  70                  75
60 ctc ggc ggc acc tgc gtc aac gtg ggc tgc atc ccc aag aag ctg atg   291
61 Leu Gly Gly Thr Cys Val Asn Val Gly Cys Ile Pro Lys Lys Leu Met
62      80                  85                  90
64 cac cag gcg gca ctg ctg gga ggc ctg atc caa gat gcc ccc aac tat   339
65 His Gln Ala Ala Leu Leu Gly Gly Leu Ile Gln Asp Ala Pro Asn Tyr
66  95                  100                 105                 110
68 ggc tgg gag gtg gcc cag ccc gtg ccg cat gac tgg agg aag atg gca   387
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RAW SEQUENCE LISTING DATE: 11/14/2001
PATENT APPLICATION: US/09/830,706 TIME: 14:12:30

Input Set : A:\55871965.app
Output Set: N:\CRF3\11142001\I830706.raw

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 69 Gly Trp Glu Val Ala Gln Pro Val Pro His Asp Trp Arg Lys Met Ala
 70                 115                 120                 125
 72 gaa gct gtt caa aat cac gtg aaa tcc ttg aac tgg ggc cac cgt gtc   435
 73 Glu Ala Val Gln Asn His Val Lys Ser Leu Asn Trp Gly His Arg Val
 74             130                 135                 140
 76 cag ctt cag gac aga aaa gtc aag tac ttt aac atc aaa gcc agc ttt   483
 77 Gln Leu Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys Ala Ser Phe
 78         145                 150                 155
 80 gtt gac gag cac acg gtt tgc ggc gtt gcc aaa ggt ggg aaa gag att   531
 81 Val Asp Glu His Thr Val Cys Gly Val Ala Lys Gly Gly Lys Glu Ile
 82     160                 165                 170
 84 ctg ctg tca gcc gat cac atc atc att gct act gga ggg cgg ccg aga   579
 85 Leu Leu Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly Arg Pro Arg
 86 175                 180                 185                 190
 88 tac ccc acg cac atc gaa ggt gcc ttg gaa tat gga atc aca agt gat   627
 89 Tyr Pro Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile Thr Ser Asp
 90                 195                 200                 205
 92 gac atc ttc tgg ctg aag gaa tcc cct gga aaa acg ttg gtg gtc ggg   675
 93 Asp Ile Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu Val Val Gly
 94             210                 215                 220
 96 gcc agc tat gtg gcc ctg gag tgt gct ggc ttc ctc acc ggg att ggg   723
 97 Ala Ser Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr Gly Ile Gly
 98         225                 230                 235
100 ctg gac acc acc atc atg atg cgc agc atc ccc ctc cgc ggc ttc gac   771
101 Leu Asp Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg Gly Phe Asp
102     240                 245                 250
104 cag caa atg tcc tcc atg gtc ata gag cac atg gca tct cat ggc acc   819
105 Gln Gln Met Ser Ser Met Val Ile Glu His Met Ala Ser His Gly Thr
106 255                 260                 265                 270
108 cgg ttc ctg agg ggc tgt gcc ccc tcg cgg gtc agg agg ctc cct gat   867
109 Arg Phe Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg Leu Pro Asp
110                 275                 280                 285
112 ggc cag ctg cag gtc acc tgg gag gac agc acc acc ggc aag gag gac   915
113 Gly Gln Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly Lys Glu Asp
114             290                 295                 300
116 acg ggc acc ttt gac acc gtc ctg tgg gcc ata ggt cga gtc cca gac   963
117 Thr Gly Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg Val Pro Asp
118         305                 310                 315
120 acc aga agt ctg aat ttg gag aag gct ggg gta gat act agc ccc gac   1011
121 Thr Arg Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr Ser Pro Asp
122     320                 325                 330
124 act cag aag atc ctg gtg gac tcc cgg gaa gcc acc tct gtg ccc cac   1059
125 Thr Gln Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser Val Pro His
126 335                 340                 345                 350
128 atc tac gcc att ggt gac gtg gtg gag ggg cgg cct gag ctg aca ccc   1107
129 Ile Tyr Ala Ile Gly Asp Val Val Glu Gly Arg Pro Glu Leu Thr Pro
130                 355                 360                 365
132 aca gcg atc atg gcc ggg agg ctc ctg gtg cag cgg ctc ttc ggc ggg   1155
133 Thr Ala Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu Phe Gly Gly
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RAW SEQUENCE LISTING DATE: 11/14/2001
PATENT APPLICATION: US/09/830,706 TIME: 14:12:30

Input Set : A:\55871965.app
Output Set: N:\CRF3\11142001\I830706.raw

```
134                370                 375                 380
136 tcc tca gat ctg atg gac tac gac aat gtt ccc acg acc gtc ttc acc   1203
137 Ser Ser Asp Leu Met Asp Tyr Asp Asn Val Pro Thr Thr Val Phe Thr
138         385                 390                 395
140 cca ctg gag tat ggc tgt gtg ggg ctg tcc gag gag gag gca gtg gct   1251
141 Pro Leu Glu Tyr Gly Cys Val Gly Leu Ser Glu Glu Glu Ala Val Ala
142     400                 405                 410
144 cgc cac ggg cag gag cat gtt gag gtc tat cac gcc cat tat aaa cca   1299
145 Arg His Gly Gln Glu His Val Glu Val Tyr His Ala His Tyr Lys Pro
146 415                 420                 425                 430
148 ctg gag ttc acg gtg gct gga cga gat gca tcc cag tgt tat gta aag   1347
149 Leu Glu Phe Thr Val Ala Gly Arg Asp Ala Ser Gln Cys Tyr Val Lys
150                 435                 440                 445
152 atg gtg tgc ctg agg gag ccc cca cag ctg gtg ctg ggc ctg cat ttc   1395
153 Met Val Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly Leu His Phe
154             450                 455                 460
156 ctt ggc ccc aac gca ggc gaa gtt act caa gga ttt gct ctg ggg atc   1443
157 Leu Gly Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala Leu Gly Ile
158         465                 470                 475
160 aag tgt ggg gct tcc tat gcg cag gtg atg cgg acc gtg ggt atc cat   1491
161 Lys Cys Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val Gly Ile His
162     480                 485                 490
164 ccc aca tgc tct gag gag gta gtc aag ctg cgc atc tcc aag cgc tca   1539
165 Pro Thr Cys Ser Glu Glu Val Val Lys Leu Arg Ile Ser Lys Arg Ser
166 495                 500                 505                 510
168 ggc ctg gac ccc acg gtg aca ggc tgc tga ggg taagcgccat ccctgcaggc 1592
W--> 169 Gly Leu Asp Pro Thr Val Thr Gly Cys Xaa Gly
170                 515                 520
172 cagggcacac ggtgcgcccg ccgccagctc ctcggaggcc agacccagga tggctgcagg 1652
174 ccaggtttgg ggggcctcaa ccctctcctg gagcgcctgt gagatggtca gcgtggagcg 1712
176 caagtgctgg acgggtggcc cgtgtgcccc acagggatgg ctcaggggac tgtccacctc 1772
178 acccctgcac ctttcagcct ttgccgccgg gcaccccccc caggctcctg gtgccggatg 1832
180 atgacgacct gggtggaaac ctaccctgtg ggcacccatg tccgagcccc ctggcatttc 1892
182 tgcaatgcaa ataaagaggg tacttttttct gaagtgtgta aaaaaaaaaa aaaaaaaaaa 1952
184 aaaaaaa                                                          1959
187 <210> SEQ ID NO: 2
188 <211> LENGTH: 521
189 <212> TYPE: PRT
190 <213> ORGANISM: Homo sapiens
192 <220> FEATURE:
193 <221> NAME/KEY: MOD_RES
194 <222> LOCATION: (520)
195 <223> OTHER INFORMATION: Selenocysteine
197 <400> SEQUENCE: 2
198 Met Ala Val Ala Leu Arg Gly Leu Gly Gly Arg Phe Arg Trp Arg Thr
199   1               5                  10                  15
201 Gln Ala Val Ala Gly Gly Val Arg Gly Ala Ala Arg Gly Ala Ala Ala
202             20                  25                  30
204 Gly Gln Arg Asp Tyr Asp Leu Leu Val Val Gly Gly Gly Ser Gly Gly
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Protein not identified in a DNA sequence OK

RAW SEQUENCE LISTING DATE: 11/14/2001
PATENT APPLICATION: US/09/830,706 TIME: 14:12:30

Input Set : A:\55871965.app
Output Set: N:\CRF3\11142001\I830706.raw

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205          35                  40                  45
207 Leu Ala Cys Ala Lys Glu Ala Ala Gln Leu Gly Arg Lys Val Ala Val
208      50                  55                  60
210 Val Asp Tyr Val Glu Pro Ser Pro Gln Gly Thr Arg Trp Gly Leu Gly
211  65                  70                  75                  80
213 Gly Thr Cys Val Asn Val Gly Cys Ile Pro Lys Lys Leu Met His Gln
214                  85                  90                  95
216 Ala Ala Leu Leu Gly Gly Leu Ile Gln Asp Ala Pro Asn Tyr Gly Trp
217             100                 105                 110
219 Glu Val Ala Gln Pro Val Pro His Asp Trp Arg Lys Met Ala Glu Ala
220         115                 120                 125
222 Val Gln Asn His Val Lys Ser Leu Asn Trp Gly His Arg Val Gln Leu
223     130                 135                 140
225 Gln Asp Arg Lys Val Lys Tyr Phe Asn Ile Lys Ala Ser Phe Val Asp
226 145                 150                 155                 160
228 Glu His Thr Val Cys Gly Val Ala Lys Gly Gly Lys Glu Ile Leu Leu
229                 165                 170                 175
231 Ser Ala Asp His Ile Ile Ile Ala Thr Gly Gly Arg Pro Arg Tyr Pro
232             180                 185                 190
234 Thr His Ile Glu Gly Ala Leu Glu Tyr Gly Ile Thr Ser Asp Asp Ile
235         195                 200                 205
237 Phe Trp Leu Lys Glu Ser Pro Gly Lys Thr Leu Val Val Gly Ala Ser
238     210                 215                 220
240 Tyr Val Ala Leu Glu Cys Ala Gly Phe Leu Thr Gly Ile Gly Leu Asp
241 225                 230                 235                 240
243 Thr Thr Ile Met Met Arg Ser Ile Pro Leu Arg Gly Phe Asp Gln Gln
244                 245                 250                 255
246 Met Ser Ser Met Val Ile Glu His Met Ala Ser His Gly Thr Arg Phe
247             260                 265                 270
249 Leu Arg Gly Cys Ala Pro Ser Arg Val Arg Arg Leu Pro Asp Gly Gln
250         275                 280                 285
252 Leu Gln Val Thr Trp Glu Asp Ser Thr Thr Gly Lys Glu Asp Thr Gly
253     290                 295                 300
255 Thr Phe Asp Thr Val Leu Trp Ala Ile Gly Arg Val Pro Asp Thr Arg
256 305                 310                 315                 320
258 Ser Leu Asn Leu Glu Lys Ala Gly Val Asp Thr Ser Pro Asp Thr Gln
259                 325                 330                 335
261 Lys Ile Leu Val Asp Ser Arg Glu Ala Thr Ser Val Pro His Ile Tyr
262             340                 345                 350
264 Ala Ile Gly Asp Val Val Glu Gly Arg Pro Glu Leu Thr Pro Thr Ala
265         355                 360                 365
267 Ile Met Ala Gly Arg Leu Leu Val Gln Arg Leu Phe Gly Gly Ser Ser
268     370                 375                 380
270 Asp Leu Met Asp Tyr Asp Asn Val Pro Thr Thr Val Phe Thr Pro Leu
271 385                 390                 395                 400
273 Glu Tyr Gly Cys Val Gly Leu Ser Glu Glu Glu Ala Val Ala Arg His
274                 405                 410                 415
276 Gly Gln Glu His Val Glu Val Tyr His Ala His Tyr Lys Pro Leu Glu
277             420                 425                 430
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RAW SEQUENCE LISTING DATE: 11/14/2001
PATENT APPLICATION: US/09/830,706 TIME: 14:12:30

Input Set : A:\55871965.app
Output Set: N:\CRF3\11142001\I830706.raw

```
279 Phe Thr Val Ala Gly Arg Asp Ala Ser Gln Cys Tyr Val Lys Met Val
280         435                 440                 445
282 Cys Leu Arg Glu Pro Pro Gln Leu Val Leu Gly Leu His Phe Leu Gly
283     450                 455                 460
285 Pro Asn Ala Gly Glu Val Thr Gln Gly Phe Ala Leu Gly Ile Lys Cys
286 465                 470                 475                 480
288 Gly Ala Ser Tyr Ala Gln Val Met Arg Thr Val Gly Ile His Pro Thr
289                 485                 490                 495
291 Cys Ser Glu Glu Val Val Lys Leu Arg Ile Ser Lys Arg Ser Gly Leu
292             500                 505                 510
W--> 294 Asp Pro Thr Val Thr Gly Cys Xaa Gly
295         515                 520
298 <210> SEQ ID NO: 3
299 <211> LENGTH: 2056
300 <212> TYPE: DNA
301 <213> ORGANISM: Homo sapiens
303 <220> FEATURE:
304 <221> NAME/KEY: CDS
305 <222> LOCATION: (188)..(1669)
307 <220> FEATURE:
308 <221> NAME/KEY: MOD_RES
309 <222> LOCATION: (493)
310 <223> OTHER INFORMATION: Selenocysteine
312 <400> SEQUENCE: 3
313 gtcccggacc tcaggcccag ttcagtgtac ttcccctctc tacttcctcc ctccagtccc 60
315 ttctccatcc ctccctttt tggctgcccc ttgcctgcct tcctcgccag tagcttgcag 120
317 agtagacacg atgacacctt ttgcaggcta aaaaggctga gagtggcact atgtgcagtg 180
319 agccacc atg gag gac caa gca ggt cag cgg gac tat gat ctc ctg gtg   229
320         Met Glu Asp Gln Ala Gly Gln Arg Asp Tyr Asp Leu Leu Val
321           1               5                  10
323 gtc ggc ggg gga tct ggt ggc ctg gct tgt gcc aag gag gcc gcc cag   277
324 Val Gly Gly Gly Ser Gly Gly Leu Ala Cys Ala Lys Glu Ala Ala Gln
325  15                  20                  25                  30
327 ctg gga agg aag gtg gcc gtg gtg gac tac gtg gaa cct tct ccc caa   325
328 Leu Gly Arg Lys Val Ala Val Val Asp Tyr Val Glu Pro Ser Pro Gln
329                  35                  40                  45
331 ggc acc cgg tgg ggc ctc ggc ggc acc tgc gtc aac gtg ggc tgc atc   373
332 Gly Thr Arg Trp Gly Leu Gly Gly Thr Cys Val Asn Val Gly Cys Ile
333              50                  55                  60
335 ccc aag aag ctg atg cac cag gcg gca ctg ctg gga ggc ctg atc caa   421
336 Pro Lys Lys Leu Met His Gln Ala Ala Leu Leu Gly Gly Leu Ile Gln
337          65                  70                  75
339 gat gcc ccc aac tat ggc tgg gag gtg gcc cag ccc gtg ccg cat gac   469
340 Asp Ala Pro Asn Tyr Gly Trp Glu Val Ala Gln Pro Val Pro His Asp
341      80                  85                  90
343 tgg agg aag atg gca gaa gct gtt caa aat cac gtg aaa tcc ttg aac   517
344 Trp Arg Lys Met Ala Glu Ala Val Gln Asn His Val Lys Ser Leu Asn
345  95                  100                 105                 110
347 tgg ggc cac cgt gtc cag ctt cag gac aga aaa gtc aag tac ttt aac   565
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Use of n and / or Xaa has been detected in the Sequence Listing. Review the Sequence Listing to ensure a corresponding explanation is present in the <220> to <223> fields of each sequence using n or Xaa.

VERIFICATION SUMMARY DATE: 11/14/2001
PATENT APPLICATION: **US/09/830,706** TIME: 14:12:31

Input Set : **A:\55871965.app**
Output Set: **N:\CRF3\11142001\I830706.raw**

L:169 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:1
L:294 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:2
L:440 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:3
L:559 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:4
L:2002 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:37
L:3285 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:38